Department of Cardiology
Faculty of Medicine
University of Helsinki
Helsinki

ELECTROCARDIOGRAPHIC AND ANGIOGRAPHIC FEATURES IN CARDIOGENIC SHOCK

Tuija Sabell

DOCTORAL DISSERTATION

To be presented for public examination with the permission
of the Faculty of Medicine of the University of Helsinki, in Lecture hall 3,
Biomedicum Helsinki 1, on the 6th of March 2020, at 12 noon
Helsinki 2020

Supervisors

Raija Jurkko, MD, PhD
Heart and Lung Center, Division of Cardiology
Helsinki University Hospital, Helsinki, Finland

Professor Markku S. Nieminen
Heart and Lung Center, Division of Cardiology
Helsinki University Hospital, Helsinki, Finland

Reviewers

Docent Tuomas Kerola
Department of Internal Medicine
Päijät-Häme Central Hospital, Lahti, Finland

Docent Pekka Porela
Heart Centre
University Hospital of Turku, Turku, Finland

Opponent

Professor Finn Gustafsson
Department of Cardiology,
Rigshospitalet University Hospital,
Copenhagen, Denmark

ISBN 978-951-51-5846-8 (paperback)
ISBN 978-951-51-5847-5 (PDF)
http://ethesis.helsinki.fi/

Unigrafia
Helsinki 2020

The Faculty of Medicine uses the Urkund system (plagiarism recognition) to examine all doctoral dissertation.

ABSTRACT

Cardiogenic shock (CS) is a medical emergency in which cardiac dysfunction causes a state of shock resulting in end-organ hypoperfusion. The most common cause of CS is acute coronary syndrome (ACS), ST-segment elevation myocardial infarction (STEMI) being the leading aetiology. Other causes of CS may include exacerbation of chronic heart failure, valvular dysfunction, myocarditis, and stress-induced cardiomyopathy. Despite progress in revascularization and development of mechanical circulatory support-devices, short-term mortality is still high at 40%, which calls for further advances in CS management and in risk stratification.

The electrocardiogram (ECG) plays a major role at the first instance of CS management, as it provides essential information about cardiac ischaemia, rhythm, and conduction. After initial evaluation, emergent coronary angiography is the next step in CS management with the possibility of immediate revascularization with percutaneous coronary intervention (PCI). The aim of this study was to examine electrocardiographic and angiographic features in CS. The patient data in this thesis are primarily included in a multinational, prospective, observational cohort study called the CardShock study, which investigated 219 CS patients with diverse CS aetiologies.

Study I evaluated baseline ECG ST-segment patterns in patients with differing CS aetiologies. ST-segment elevation was associated with ACS, and in patients with ST-segment elevation, CS was often the first manifestation of coronary artery disease. One-third of patients with ST-segment depression did not have ACS, but ST-segment depression was associated with a high burden of previous comorbidities. ST-segment elevation was associated with 90-day mortality in patients with mixed CS aetiologies. In the subgroup of ACS patients, no difference in revascularization or mortality rates emerged between the studied ST-segment patterns.

Study II examined ventricular conduction disturbances in patients with ACS-related CS. In this population, ventricular conduction disturbances occurred more often in older patients with a higher burden of comorbidities. The temporal evolution of ventricular conduction blocks from baseline to day three was high, because one-third of the blocks were transient. All ventricular conduction disturbances were associated with poor prognosis, and the reversal of the block during the first three days was not associated with better one-year survival.

Study III examined the prognostic value of the SYNTAX scores in STEMI-related CS patients. The SYNTAX score is a tool created for assessment of the complexity of coronary artery disease. In this study, SYNTAX score was calculated before PCI (baseline SYNTAX score) and after PCI (residual SYNTAX score). The baseline SYNTAX score was associated

with mortality, but its additive value in risk prediction beyond clinical assessment and risk scores was marginal. Residual SYNTAX score did not associate with outcome in STEMI-related CS.

Study IV examined angiographic features and their prognostic value in ACS-related CS. Multivessel disease and unsuccessful revascularization of the infarct-related artery were associated with poor prognosis. In addition, assessment of procedural PCI complications showed that arrhythmic complications were the most common, but they did not associate with worse outcome.

In conclusion, electrocardiography is an important tool for differentiating the aetiologies of CS and it can be useful in risk assessment. ST-segment elevation and ventricular conduction blocks are markers of high mortality risk. In addition, some angiographic features may prove useful in prognosis assessment. Multivessel disease carries a high mortality risk, whereas successful revascularization of the infarct-related artery is associated with better outcome.

TIIVISTELMÄ

Sydänperäinen shokki on lääketieteellinen hätätilanne, jossa äkillinen sydämen vajaatoiminta aiheuttaa elimistön yleisen shokkitilan ja verenkierron vajauksen. Sepelvaltimotautikohtaus on yleisin sydänperäisen shokin aiheuttaja. Useimmiten potilaalla todetaan ST-nousuinfarkti. Sydänperäisen shokin muita syitä voivat olla kroonisen sydämen vajaatoiminnan pahenemisvaihe, sydänläppien viat, sydänlihastulehdus tai järkytyksen aiheuttama sydänhalvaus. Sydänperäisen shokin hoitomuotojen kehityksestä huolimatta sairauden kuolleisuus on korkea, sillä jopa puolet potilaista menehtyy sairaalahoidon aikana. Sydänperäisen shokin huono ennuste peräänkuuluttaakin edistysaskelia sydänperäisen shokin hoidossa ja riskin arviossa.

Sydänsähkökäyrä on keskeinen työkalu sydänperäisen shokin diagnostiikassa ensihetkistä lähtien. Sydänsähkökäyrä antaa tietoa sydänlihaksen hapenpuutteesta ja mahdollisista rytmi- ja johtumishäiriöistä. Ensiarvion jälkeen kaikille sydänperäistä shokkia sairastaville potilaille tulisi tehdä kiireellinen sepelvaltimoiden varjoainetutkimus. Varjoainetutkimuksessa voidaan todeta tukkeutunut sepelvaltimo ja hoitaa se pallolaajennuksella. Tämän väitöskirjan tavoitteena on tutkia neljässä eri osatyössä sydänsähkökäyrän muutoksia ja sepelvaltimoiden varjoainetutkimuksen löydöksiä sydänperäisessä shokissa. Väitöskirjan potilasmateriaali on pääosin peräisin 219 potilaan CardShock tutkimuksesta, joka on sydänperäisen shokin etenevä ja havainnoiva monikeskustutkimus.

Osatyössä I tutkittiin sisäänottovaiheen sydänsähkökäyrien ST-tasojen muutoksia. ST-nousupotilailla sepelvaltimotautikohtaus oli yleisimmin shokin aiheuttaja ja sydänperäinen shokki oli usein sepelvaltimotaudin ensimmäinen ilmentymä. Yhdellä kolmasosalla ST-laskupotilaista shokin syy oli muu kuin sepelvaltimotautikohtaus. ST-lasku oli kuitenkin yhteydessä suurempaan todennäköisyyteen sairastaa liitännäissairauksia. Koko tutkimuskohortissa ST-nousu oli yhteydessä huonoon ennusteeseen. Sepelvaltimotautikohtauspotilaat hoidettiin pallolaajennuksella yhtä usein ST-tason muutoksista huolimatta, eikä eroa kuolleisuudessa todettu.

Osatyössä II arvioitiin kammiojohtumisen häiriöitä potilailla, joilla oli sepelvaltimotautikohtauksesta johtuva sydänperäinen shokki. Kammiojohtumisen häiriöt olivat yleisiä ja ne olivat yhteydessä korkeampaan ikään ja suurempaan riskiin sairastaa liitännäissairauksia. Kammiojohtumisen häiriöt olivat usein ohimeneviä, sillä jopa puolet todetuista kammiojohtumisen häiriöistä hävisivät tai muuttuivat toiseksi häiriöksi kolmen päivän seurannan aikana. Kammiojohtumisen häiriöt liittyivät huonompaan ennusteeseen, sillä kaikki eri kammiojohtumisen häiriön muodot olivat yhteydessä korkeampaan kuolleisuuteen, eikä myöhempi johtumisen korjaantuminen parantanut ennustetta.

Osatyössä III selvitettiin SYNTAX scoren ennusteellista merkitystä ST-nousuinfarktin aiheuttamassa sydänperäisessä shokissa. SYNTAX score on työkalu, jolla voidaan arvioida sepelvaltimotaudin vaikeusastetta. Tässä tutkimuksessa SYNTAX score laskettiin ennen sepelvaltimoiden pallolaajennusta (baseline SYNTAX score) ja pallolaajennuksen jälkeen (residual SYNTAX score). Baseline SYNTAX score oli yhteydessä korkeampaan kuolleisuuteen, mutta sen tuoma lisäarvo riskinarviossa kliinisten tekijöiden ja riskilaskureiden ohella oli rajallinen. Residual SYNTAX scorella ei ollut merkitystä ennusteen arviossa.

Osatyössä IV selvitettiin sepelvaltimoiden varjoainekuvauksen löydösten ennusteellista merkitystä sepelvaltimotautikohtauksen aiheuttamassa sydänperäisessä shokissa. Monisuonitauti ja epäonnistunut verenkierron palautuminen pallolaajennuksen jälkeen liittyivät huonoon ennusteeseen. Lisäksi tutkittiin pallolaajennuksen aikaisia komplikaatioita, joista rytmihäiriöt olivat yleisimpiä; niiden esiintyminen ei kuitenkaan huonontanut ennustetta.

Yhteenvetona voidaan todeta, että sydänsähkökäyrä on tärkeä työväline sydänperäisen shokin aiheuttajan ja ennusteen arvioinnissa. ST-nousu ja kammiojohtumisen häiriöt ovat yhteydessä korkeaan kuolleisuuteen. Sepelvaltimoiden varjoainekuvauksen löydöksistä osa on hyödyllisiä sydänperäisen shokin ennusteen arvioinnissa. Monisuonitauti on huonon ennusteen merkki, kun taas onnistunut verenkierron palautuminen pallolaajennuksen yhteydessä on yhteydessä parempaan ennusteeseen.

ACKNOWLEDGEMENTS

This thesis was carried out at the Heart and Lung Center of Helsinki University Hospital between 2015 and 2020. I have been lucky to be a part of our exquisite Acute Heart Failure study group, which has offered me scientific enthusiasm, unparalleled peer support, international aspects, and most importantly, many close colleagues.

I am deeply grateful to my supervisor Raija Jurkko, who introduced me to the world of cardiology and invited me to join our study group. I have always admired her relentless attitude towards work and marvelled at her never-ending energy. She has led me through this thesis and taught me much about the scientific way of thinking. Her knowledge of electrocardiography has been of key value in this thesis. I am grateful that she took me under her wing and inspired me to my career path, both in science and in clinical medicine.

I warmly thank my second supervisor Markku S. Nieminen, Emeritus Professor of Cardiology, for his guidance throughout this project. I was honoured to become his PhD student. His vast expertise in cardiology and of heart failure has been invaluable, and his esteemed career is an inspiration to me.

My warmest appreciation goes to the Acute Heart Failure study group leaders Docent Veli-Pekka Harjola and Docent Johan Lassus. Docent Harjola, the primary investigator for the CardShock study, has always encouraged me and has offered me precious advice in writing and in refining my studies. Docent Lassus has been irreplaceable with his inspiring ideas and firm guidance both in science and in the clinical world. I think highly of his excellent managerial skills in Jorvi Hospital, where I have had the privilege to work under his supervision. The many research leaves that he granted have made it possible for me to finish this thesis during the last year.

My dear colleague and co-author Heli Tolppanen deserves my heartfelt thanks for continuous support and being an inspirational mentor. She has helped me from the very beginning with the statistical analyses and thereafter with all imaginable matters from applying for research grants to helping me

arrange my research exchange in Paris. Her help has been crucial to me, and I value our friendship highly.

The Acute Heart Failure study group has given me invaluable support and joy. My warmest thanks go to young doctors Tuukka Tarvasmäki for his steady guidance and good company, to Toni Jäntti for his humour and gastronomic flare, and to Anu Kataja and Mari Hongisto for their lively encouragement. Our shared congress trips are some of the fondest memories of this project.

I offer my sincere thanks to all my co-authors. A special mention goes to Marjut Varpula for her remarkable effort. Besides my Finnish colleagues, I am deeply grateful to Professor Alexandre Mebazaa, who invited me to join his research team in Paris. Under his close supervision, I learned a great deal about the scientific world. I extend my gratitude to all my colleagues in Paris and especially to Lithuanian Kamile Čerlinskaitė who shared the everyday work and challenges in R with me.

The pre-examiners, Docents Tuomas Kerola and Pekka Porela, deserve my warmest thanks for their constructive and thorough review. They saw the big picture and helped me to construct this thesis into a more coherent entity. I also thank Professor Kjell Nikus and Docent Hannu Parikka for being part of my thesis committee. Carol Norris deserves warm thanks for her great effort in correcting my language and providing me with end focus.

The scientific work for this thesis was financed by our heart failure study group via scholarships from the Aarne Koskelo Foundation and The Finnish Medical Foundation, and by personal grants from the Finnish Cardiac Society, the Paavo Ilmari Ahvenainen Foundation, and the Paavo Nurmi Foundation. The travel grants from the Finnish Cardiac Society, Finska Läkaresällskapet, and the University of Helsinki made the unforgettable congress trips possible.

I thank all my seniors and colleagues during my clinical residency. My special praise goes to all the residents in Lohja for encouraging me in my scientific aspirations and for making the beginning of my career cheerful. I am also thankful for all the research leaves and possibilities to attend international congresses during my time in Lohja. My warm thanks go to my

current colleagues in Jorvi, who have made me feel that I belong. Naturally, I owe my heartfelt affection to all my close friends who have supported me and also taken my mind off research during these years. Special gratitude goes to my oldest friend Anna, who has encouraged me to do my best from our first school years and still is one of the most important persons in my life.

My deepest gratitude goes to my parents, for their boundless love and support. The one reason for the swift progress of this thesis are solely the periods spent in our cottage with my father Mikko, who has made the circumstances optimal for my research. Work, exercise, sauna, and sleep; and repeat. Sauna-Tuija has never been as happy as in the research weeks in Makitsu. I am also grateful to my mother Tarja, from whose example I have learned a straightforward attitude towards work. Furthermore, she has always made me feel loved and valuable. I am also thankful to my parents-in-law Ulla and Hannu and to the families of Petri and Sakari for their continuous support.

My gratitude overflows to my sister, best friend, and role model Mervi. We have shared our lives, and she has given me peer PhD student support at every step of the way. I have always looked up to her, and she has always had it in her heart to encourage me. My distinct thanks go also to her family, her brilliant husband Miikka, and especially to Tacu and Mölli, two furry fellows who always make my spirit lighter and who have cheered me with their barking to carry on my work.

In the end, my husband Marco, you are my everything. You have given me strength and tangible everyday support to carry on with this project. You have never wavered in the face of the duties fallen into your lap because I was busy with my research, and you have been excellent in taking my mind off this project when necessary. It is impossible to describe in words all the encouragement and encompassing love that you have surrounded me with throughout these years.

Helsinki, February 2020

Tuija Sabell

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I Javanainen T, Tolppanen H, Lassus J, Nieminen MS, Sionis A, Spinar J, Silva-Cardoso J, Greve Lindholm M, Banaszewski M, Harjola VP, Jurkko R. Predictive value of the baseline electrocardiogram ST-segment pattern in cardiogenic shock: Results from the CardShock Study. Ann Noninvasive Electrocardiol. 2018 Sep;23(5): e12561.

II Tolppanen H, Javanainen T, Sans-Rosello J, Parenica J, Nieminen T, Pavlusova M, Masip J, Köber L, Banaszewski M, Sionis A, Spinar J, Harjola VP, Jurkko R, Lassus J. Prevalence, Temporal Evolution, and Impact on Survival of Ventricular Conduction Blocks in Patients With Acute Coronary Syndrome and Cardiogenic Shock. Am J Cardiol. 2018 Jul 15;122(2):199-205.

III Javanainen T, Sans-Roselló J, Harjola VP, Nieminen MS, Lassus J, Sionis A, Varpula M, Jurkko R. Prognostic impact of baseline and residual SYNTAX scores in cardiogenic shock. Catheter Cardiovasc Interv. 2019 Jan 1;93(1):1-8.

IV Sabell T, Banaszewski M, Lassus J, Nieminen MS, Tolppanen H, Jäntti T, Kataja A, Hongisto M, Køber L, Sionis A, Parissis J, Tarvasmäki T, Harjola VP, Jurkko R. Prognostic impact of angiographic findings, procedural success and timing of percutaneous coronary intervention in cardiogenic shock. Accepted for publication in ESC Heart Failure.

The publications are referred to in the text by their roman numerals. The original publications are reprinted with permission of the copyright holders.

ABBREVIATIONS

ACS	acute coronary syndrome
AUC	area under the curve
AV	atrioventricular
BPM	beats per minute
CABG	coronary artery bypass grafting
CRP	C-reactive protein
CS	cardiogenic shock
CULPRIT-SHOCK	Culprit Lesion Only PCI Versus Multivessel PCI in Cardiogenic Shock
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eGFR	estimated glomerular filtration rate
GUSTO I	The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries I
HR	hazard ratio
Hs-TnT	high-sensitive troponin T
IABP	intra-aortic balloon pump
IABP-SHOCK II	Intraaortic Balloon Pump in Cardiogenic Shock II
IRA	infarct-related artery
IQR	interquartile range
IVCD	unspecified intraventricular conduction delay
LAD	left anterior descending
LAHB	left anterior hemiblock
LBBB	left bundle branch block
LCX	left circumflex
LM	left main
LPHB	left posterior hemiblock
LVAD	left ventricular assist device
LVEF	left ventricular ejection fraction
MAP	mean arterial pressure
MCS	mechanical circulatory support
NSTD	No ST-segment deviation or ST-segment impossible to analyse
NSTEMI	non-ST-segment elevation myocardial infarction
NT-proBNP	N-terminal pro-natriuretic peptide
PCI	percutaneous coronary intervention
PCWP	pulmonary capillary wedge pressure
RBBB	right bundle branch block
RCA	right coronary artery
ROC	receiver operating characteristic
SBP	systolic blood pressure

SD	standard deviation
SHOCK	SHould we emergently revascularize Occluded Coronaries for cardiogenic shock
STDEP	ST-segment depression
STE	ST-segment elevation
STEMI	ST-segment elevation myocardial infarction
SVG	saphenous vein graft
TIMI	Thrombolysis in Myocardial Infarction
VCB	ventricular conduction block

1 INTRODUCTION

Cardiogenic shock (CS) is a medical emergency in which cardiac dysfunction causes a state of shock resulting in end-organ hypoperfusion. The most common aetiology of CS is acute coronary syndrome (ACS) (1,2). Other causes include exacerbation of chronic heart failure, valvular dysfunction, stress-induced cardiomyopathy, and myocarditis (3). In the last four decades, short-term mortality rates of CS have decreased from 80% to the current 40% (1,4,5), mainly due to increased use of revascularization strategies. Despite progress in reperfusion therapies and in modern intensive care, in-hospital mortality is still unacceptably high, and advances in management and risk stratification are necessary.

The electrocardiogram (ECG) is an important diagnostic tool in CS. In an acute setting, ST-segment deviations, i.e. ST-segment elevation (STE) and ST-segment depression (STDEP), often raise the idea of myocardial ischaemia and acute myocardial infarction. ST-segment deviations can, however, also be chronic changes resulting from left ventricular hypertrophy (6), or be acute changes resulting from other cardiac diseases such as myocarditis or stress-induced cardiomyopathy (7,8). In CS patients, ST-segment deviations have only been studied in the context of ACS, mostly by dividing patients into two established categories: ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation myocardial infarction (NSTEMI). Separate data on patients with STE and STDEP and on patients without ST-segment changes (NSTD), are, however, scarce. ST-segment deviations, in particular, have not been studied in patients with CS aetiologies other than ACS.

In addition to ST-segment levels, analysis of QRS configuration and duration is important in patients with acute cardiac distress, because acute changes in the QRS complex may be attributable to severe myocardial ischaemia (9). In ACS, bundle branch block in the baseline ECG has been associated with high incidence of CS (10–13) and with increased short- and long-term mortality (11,12,14–16). In the context of myocardial ischaemia, conduction disturbances are often transient (17,18), with a high frequency of block resolution being described in patients with ACS (16,19). Previously, resolution of ventricular conduction disturbances has been associated with better outcome (12,16). A few studies in CS patients have shown that prolonged QRS (20) and right bundle branch block (RBBB) are associated with worse survival (11,21), but other ventricular conduction disturbances such as fascicular hemiblocks and unspecified intraventricular conduction delay (IVCD), and temporal evolution of the ventricular conduction blocks, have been neglected in the context of ACS-related CS.

Because ACS is the most common aetiology of CS, emergent coronary angiography and revascularization are essential in CS management. In addition to treatment with percutaneous coronary intervention (PCI),

coronary angiography provides information about coronary anatomy and the extent of coronary artery disease. Previously in ACS-related CS, multivessel- (22–24) and three-vessel coronary artery disease (25–28), left main (LM) coronary artery as the infarct-related artery (IRA) (23,25,27), and unsuccessful revascularization of the IRA (23–25,27–31) have been associated with worse outcome. Many of these studies, however, predated the primary PCI era (25–27), were of a retrospective design (30,32), or examined registry data (23,28,31). Complications during PCI in patients with ACS are fairly common (33), but data are scarce on procedural complications and on their effect on outcome in ACS-related CS.

The SYNTAX score is an angiographic scoring tool calculated from coronary angiograms defining the extent of coronary artery disease. The baseline SYNTAX score is calculated before PCI, and it reflects the burden of coronary artery disease. The residual SYNTAX score is calculated after PCI and can serve as a tool to evaluate completeness of revascularization. Both SYNTAX scores have been associated with outcome in patients with ACS (34–39), but they have not been studied in CS.

The aim of this thesis is to study electrocardiographic changes and features of coronary angiography in CS patients primarily included in a prospective, observational, multinational study of CS called the CardShock study.

2 REVIEW OF THE LITERATURE

2.1 Cardiogenic shock

2.1.1 Diagnosis and classification

Cardiogenic shock (CS) is the most severe form of heart failure, a state of inadequate tissue- and end-organ perfusion resulting from primary cardiac dysfunction (40). Diagnostic criteria for CS include persistent hypotension unresponsive to volume replacement (systolic blood pressure [SBP] < 90 mmHg) in combination with clinical hypoperfusion (cold extremities, oliguria, mental confusion, dizziness, and narrow pulse pressure) (41). Laboratory measures associated with hypoperfusion are metabolic acidosis, elevated serum lactate, and elevated serum creatinine (41).

Though CS diagnosis is based on clinical findings, objective invasive haemodynamic parameters can serve in confirming the diagnosis. The Forrester classification of acute heart failure was developed in patients with acute myocardial infarction, categorising patients into four haemodynamic groups by measurements of cardiac index and pulmonary capillary wedge pressure (PCWP) (Figure 1) (42). The classification of acute heart failure can also be made without invasive testing, based on bedside physical examination. The aim is to detect the presence of clinical signs of congestion ('wet' vs. 'dry') and peripheral hypoperfusion ('cold' vs. 'warm') (41,43). In classic CS, the cardiac index is low (< 2.2 L/min/m^2), PCWP is elevated (> 18 mmHg), and systemic vascular resistance is high, clinically corresponding to the 'wet' and 'cold' profile (3,42). Figure 2 describes other haemodynamic phenotypes of CS, in which a low cardiac index is present in them all, but ventricular preload, volume, and systemic vascular resistance may vary (3). A haemodynamically distinct entity is right ventricular CS, in which patients can be normotensive with peripheral hypoperfusion, haemodynamically characterized by relatively higher central venous pressures, higher left ventricular ejection fraction (LVEF), and lower pulmonary artery systolic pressures, with no difference in PCWP (3).

The clinical manifestation of CS at presentation ranges from mild hypoperfusion to profound shock and a pulseless state (44). Refractory CS can be defined as ongoing evidence of tissue hypoperfusion despite administration of adequate doses of two vasoactive medications and appropriate treatment of the underlying aetiology (45).

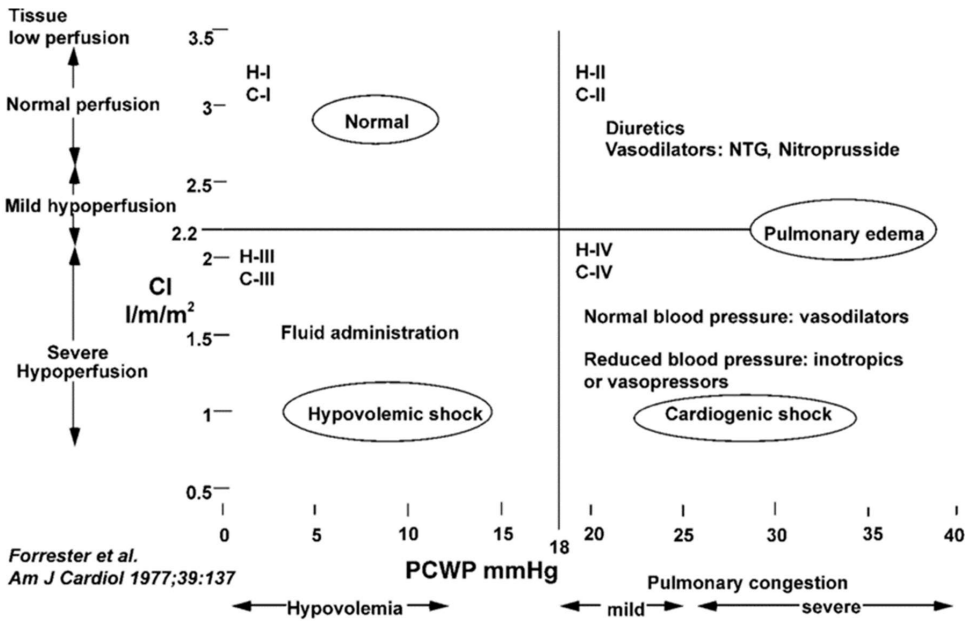


Figure 1 Forrester classification of heart failure. H I-IV refers to haemodynamic severity, C I-IV refers to clinical severity. Abbreviations: CI = cardiac index, PCWP = pulmonary capillary wedge pressure. Reproduced with the permission of Oxford Academics (46).

https://www.ahajournals.org/doi/10.1161/CIR.0000000000000525

Figure 2 Haemodynamic presentations of cardiogenic shock. Abbreviations: CI = cardiac index, PCWP = pulmonary capillary wedge pressure, SVRI = systemic vascular resistance index. Reproduced with the permission of Wolters Kluwer (3).

2.1.2 Aetiology

Acute cardiac haemodynamic instability can result from disorders worsening the function of the myocardium, valves, conduction system, or pericardium, either in isolation or in combination. The most common aetiology is acute coronary syndrome (ACS) in 50% to 80% of the cases (2,47). ACS is due to decreased blood flow in the coronary arteries, resulting in myocardial ischaemia and myocardial infarction. Type 1 myocardial infarction results from atherothrombotic coronary artery disease and is usually precipitated by atherosclerotic plaque disruption. Type 2 myocardial infarction results from the imbalance of oxygen supply and demand in the myocardium (48). The three main clinical manifestations of ACS defined by electrocardiographic findings are STEMI, NSTEMI, and unstable angina. ACS diagnosis is based on symptoms, electrocardiographic findings, troponin elevations, and imaging. In CS, STEMI predominates as the main cause, followed by NSTEMI (1,2). In the context of ACS, the cause of CS can also be a mechanical complication, such as rupture of a papillary muscle, of the ventricular septum, or of the ventricular free wall (40). In addition, acute severe mitral regurgitation, caused by papillary muscle dysfunction due to papillary muscle ischaemia, can be the cause of CS (46).

The second most common cause of CS is exacerbation of chronic heart failure (3). Other, more rare causes are for example valvular dysfunction, myocarditis, stress-induced cardiomyopathy, pulmonary embolism, peri-partum cardiomyopathy, cardiac tamponade, cardiac constriction, or dynamic outflow tract obstruction. In addition, CS can be iatrogenic, caused by excessive or too-early treatment with beta-blockers or angiotensin-converting enzyme inhibitors or by excess volume loading in right ventricular failure (40).

2.1.3 Pathophysiology

CS is a result of temporary or permanent haemodynamic disturbances in the heart and in the entire circulatory system. Depressed myocardial contractility results in a detrimental vicious cycle of reduced cardiac output, low blood pressure, and reduced flow in the coronary arteries, all leading to further coronary ischaemia and additional reduction in myocardial contractility (40). Myocardial stunning is a phenomenon resulting from an episode of intense ischaemia and subsequent reperfusion. This condition is characterized by a post-ischaemic perfusion-contraction mismatch in which contractile function remains severely depressed despite normal myocardial blood flow (49). Myocardial stunning is regarded as reversible, but in patients with myocardial infarction, it can contribute to the development of CS. In addition to myocardial stunning, evidence exists of vascular, metabolic, neuronal, and electrical stunning in the post-ischaemic phase (50). In addition, decreased

left ventricular function and myocardial ischaemia causes deterioration of diastolic function, leading to elevation in left arterial pressure and consequently to pulmonary congestion, hypoxia, and worsening ischaemia (45).

The cascade of worsening systolic and diastolic dysfunction provokes compensatory mechanisms that are often maladaptive and further lead to a progressive downward spiral of worsening shock. The compensatory mechanisms include systemic vasoconstriction that may initially improve coronary and peripheral perfusion, but subsequently causes increased cardiac afterload, which overburdens the already damaged myocardium (51). Hypoperfusion causes activation of the sympathetic system, i.e. the release of catecholamines, which improves myocardial contractility and peripheral blood flow, but also causes increased myocardial oxygen demand and has proarrhythmogenic effects (40). Activation of compensatory neurohormonal responses leads to upregulation of the renin-angiotensin system, which causes increased preload, systemic vasoconstriction, and fluid retention (52). In addition, inflammatory response mechanisms are stimulated, resulting in the release and activation of inducible nitric oxide synthase and peroxynitrite, which stimulate pathological vasodilatation and have cardiotoxic and negative inotropic effects (53–56). Furthermore, increased levels of interleukins have been associated with higher mortality (57). And, extensive inflammatory response, even without concomitant infection, is associated with worse CS outcome (58). Taking into account the complexity of CS mechanisms, it is not surprising that severe impairment of left ventricular contractility does not always cause CS, and conversely, in CS, LVEF may only be moderately depressed, for example in those with acute aortic or mitral regurgitation (59).

2.1.4 Epidemiology

In the context of ACS, CS incidence ranges from 3% to 14% (4,10,31,60–64). This relatively wide range reflects different CS definitions, different patient profiles, and different time periods, and no clear tendency towards increase or decrease in CS incidence emerges in these studies. In the majority of ACS patients, CS is not present at hospital admission; it occurs most often during the first 24 hours of hospitalisation (1,10,60,61). ACS patients who develop CS are older and more often female. They also have more comorbidities and more often suffer from anterior myocardial infarction when compared to ACS patients without CS (62,64–66). In acute heart failure, CS incidence ranges from 2% to 7% (67–71); data on other CS aetiologies are scarce. The incidence of CS in stress-induced cardiomyopathy is reportedly around 10% (72–74).

2.1.5 Prognosis

Within four decades, short-term mortality rates in CS have decreased from 80% to the current 35% to 50% (1,4,31,61,71,75,76). Development of medical treatment and especially introduction of revascularization strategies have been key components in improvement of CS prognosis up to the beginning of the 21st century (77). Regardless of improved revascularization strategies and the introduction of mechanical support devices, no substantial decline in mortality rates has, however, been evident during the past 15 years (1,31). In general, mortality rates in CS are highest during hospitalisation (31,78). After hospital discharge, the mortality rates from CS in comparison to those from ACS were higher up to 60 days, but thereafter survival rates were similar (79). Indeed, if a CS patient survives from the acute phase, long-term survival approximates that of ACS patients without CS (80).

Several biological and clinical factors are under study for prognosis assessment in CS. Risk stratification tools incorporate these factors into risk scores. The GRACE risk score, which includes eight predictors of death and was developed for patients with ACS, has good discrimination for in-hospital and long-term mortality, but is not applicable to CS patients without ACS (81,82). Two risk-prediction tools for in-hospital mortality in CS have been derived from randomized trials of CS: the Sleeper score from the SHOCK (SHould we emergently revascularize Occluded Coronaries for cardiogenic shock) trial cohort including eight items (83) and the IABP-SHOCK II risk score from the IABP-SHOCK II (Intraaortic Balloon Pump in Cardiogenic Shock II) trial cohort with six items (84). In addition, we present in detail a risk score created from the CardShock Study population (85), in the methods section. Table 1 describes the factors included in the above-mentioned risk scores.

Table 1 Clinical covariates included in different risk scores

	GRACE 2003	Sleeper 2010	CardShock 2015	IABP-SHOCK II 2017
Higher age	x	x	x	x
ACS aetiology for CS			x	
Systolic blood pressure	x	x		
Heart rate	x			
Arterial lactate			x	x
Glucose (> 10.6 mmol/L or 191 mg/dL)				x
Creatinine or eGFR	x	x	x	x
LVEF			x	
Cardiac arrest at admission	x			
STE on ECG	x			
Abnormal cardiac enzymes/markers	x			
Killip class	x			
Shock on admission		x		
Clinical signs of end-organ hypoperfusion		x		
Anoxic brain damage / confusion		x	x	
Prior myocardial infarction/CABG		x	x	
Non-inferior myocardial infarction		x		
Prior stroke				x
TIMI < 3 flow post-PCI				x

Abbreviations: ACS = acute coronary syndrome, CABG = coronary artery bypass grafting, CS = cardiogenic shock, ECG = electrocardiogram, eGFR = estimated glomerular filtration rate, LVEF = left ventricular ejection fraction, PCI = percutaneous coronary intervention, SBP = systolic blood pressure, STE = ST-segment elevation

2.2 Management of cardiogenic shock

2.2.1 Initial evaluation and patient monitoring

Patients with suspected CS should undergo immediate comprehensive assessment (41). The electrocardiogram (ECG) is the first tool to discriminate between myocardial ischaemia and other possible CS causes such as conduction disturbances (3,86). Echocardiography is required immediately, primarily for evaluation of left and right ventricular function, for valve dysfunction, and also for possible diagnosis of mechanical complications of ACS (44). If ACS is suspected, immediate coronary angiography is recommended, and in the case of mechanical complication, immediate surgical treatment is indicated (87). All CS patients should be transferred to a tertiary care center, with 24/7 service of cardiac catheterization and a dedicated intensive or cardiac care unit with a possibility of short-term mechanical circulatory support (41).

Continuous telemetry, arterial blood pressure monitoring, and central-vein pressure monitoring are suggested (3), but with no clear evidence for the optimal method of haemodynamic monitoring (41). Randomized studies and meta-analyses have failed to show the benefit in using a pulmonary artery catheter in critically ill patients (88–90). Based on recommendations of CS management, the pulmonary artery catheter is not a routine recommendation, but it is an option in selected patients with severe CS (3,41,44). In general, evaluation of the adequacy of end-organ and tissue perfusion requires integrating serial markers of systemic perfusion, which include arterial lactate, mixed or central venous oxygen saturations, urine output, creatinine, liver-function tests, mental status, temperature, and invasive haemodynamic variables, including pulmonary artery catheter measurements, especially if initial therapy is unsuccessful (3).

2.2.2 Haemodynamic management and vasoactive medications

In CS, at least relative hypovolemia is common. The first line of treatment of hypotension is fluid challenge (> 200 ml of fluid within 15-20 minutes) to correct hypovolemia and to optimize right ventricular preload in order to elevate cardiac output, especially if no overt fluid overload is present (41,91,92) Setting one target limit for mean arterial pressure (MAP) is challenging, since CS is a haemodynamically heterogeneous disorder in which haemodynamic measurements may not adequately reflect end-organ blood flow or tissue perfusion (3). An initial target for MAP of over 65 to 70 mmHg is what most experts consider adequate (93). Unless fluid therapy corrects the haemodynamic instability, vasoactive treatment should be commenced to restore adequate perfusion pressure and cardiac output.

The most used vasopressors are catecholamines, which act through adrenergic α and β receptors. In the current guidelines, noradrenaline is the choice over dopamine (3,41), since some evidence exists that noradrenaline may be associated with better outcome in shock patients, dopamine being associated with a higher rate of arrhythmias (94). Use of adrenaline is only reserved for resuscitation and may be considered in refractory shock (41), because adrenaline may be associated with excess CS mortality (95–97). Although necessary for optimization of haemodynamic instability, catecholamines produce adverse effects. They cause vasoconstriction, which may worsen myocardial ischaemia and impair tissue microcirculation. In addition, catecholamines elevate the demand for myocardial oxygen and can trigger arrhythmias (98,99). All efforts are essential to minimize vasoactive medications; all of them should be administered at the lowest dose and for the shortest period possible (45).

Another type of vasoactive medications comprises inotropic agents, whose role is to enhance myocardial contractility and vasodilatation. Dobutamine is the most commonly recommended inotrope (41,44), a synthetic catecholamine with its predominant effect via β_1 stimulation, resulting in increased heart rate and contractility (99). Levosimendan is a calcium sensitizer, which induces inotropy by calcium sensitization of contractile proteins in the cardiac myocytes (100). A recent Cochrane review of 13 trials showed that levosimendan may result in better short-term outcome than dobutamine but found no evidence of long-term benefit (101). Milnirone is a PDE3 inhibitor that raises intracellular cAMP and thus has inotropic effects independent of those of β receptors. One retrospective study comparing dobutamine and milrinone found no differences between them in haemodynamic changes or in the extent of the resultant hypotension, whereas the use of concomitant vasoactive medications was similar between the groups. Milrinone was more often discontinued because of hypotension, and dobutamine because of arrhythmia (102).

2.2.3 Mechanical circulatory support

In refractory CS, mechanical circulatory support (MCS) may be considered to improve haemodynamics, to maintain adequate perfusion pressure and to prevent multiorgan failure. Previously, the intra-aortic balloon pump (IABP) was the most widely used MCS in CS in up to 45% of ACS-related CS patients (1,61,103) and even in 82% of the patients in refractory shock (104). International recommendations for IABP utilization were, however, downgraded after publication of the IABP-SHOCK II trial, which showed no survival benefit with IABP in ACS-related CS, either in short- or in long-term follow-up (105–107). A recent Cochrane review also found similar results (108). Currently, IABP is not routinely recommended for CS, but may be

considered for haemodynamic support in selected patients, for example in the context of a mechanical complication of myocardial infarction (41,109).

Other MCS include left ventricular assist devices (LVAD) and extracorporeal circulatory support. With the lack of IABP benefit, the rate of active MCS use has increased (2). In theory, MCS can permit haemodynamic stabilization, which may interrupt the vicious spiral of hypotension, myocardial dysfunction, and myocardial ischaemia (110). One hypothesis is, however, that the artificial contact with these devices in fact promotes systemic inflammatory response (3). In addition, bleeding complications are common with MCS (111). A recent meta-analysis including four randomized trials showed no improvement in mortality with the use of an LVAD versus an IABP (111). Current guidelines recommend that MCS may only be considered in refractory shock (109). Indeed, MCS utilization relies mainly on individual experience of dedicated centres in carefully selected patients and each MCS application should be a decision of a multidisciplinary team (112).

Extracorporeal circulatory support devices such as veno-arterial extracorporeal membrane oxygenation (va-ECMO) has good potential in CS, since it offers both cardiac and respiratory support (110). Small studies have described increased CS survival with the use of an ECMO in comparison with an IABP (113), but not with an LVAD (114,115). A clinical problem with using ECMO in CS is the marked increase in left ventricular afterload, causing pulmonary oedema, left ventricular dilation, stasis, and finally thrombus formation (116). To overcome this complication, some centres have begun the combined use of ECMO and LVAD (117,118).

2.3 Coronary angiography and revascularization in cardiogenic shock

2.3.1 Extent of coronary artery disease

The blood supply to the myocardium is provided by the three main coronary arteries. The right coronary (RCA) artery originates directly from the root of the aorta, as does the left main (LM) coronary artery. The LM coronary artery then divides into its two main branches called the left anterior descending coronary artery (LAD) and the left circumflex artery (LCX). The LAD supplies the anterolateral myocardium, apex, and interventricular septum. The LCX supplies the posterolateral ventricle, and the RCA supplies the right ventricle and the posterior wall of the left ventricle, but the territories of the LCX and RCA may differ, due to the dominance of either vessel. A significant coronary obstruction is defined as ≥ 50% angiographic diameter stenosis in the epicardial coronary arteries (119).

The majority of CS patients have multivessel coronary artery disease (22–28,120–122), a condition associated with higher mortality than one-vessel disease (22,23,25–28). The percentages of the infarct-related arteries

(IRAs) have been reported as the following: LM in approximately 6%, LAD in 40%, LCX in 10% to 15%, RCA in 30% to 40%, and a bypass graft in 2% to 8% (23,25,27). The LM as the IRA has been associated with poor outcomes (23,25,27,31), whereas the RCA has been associated with better survival (26,32). One study reported no difference in mortality between different culprit arteries, but showed that distal lesions were associated with higher mortality than were proximal lesions (24). In addition, chronic total occlusion in a non-IRA has been associated with poor outcomes (22,123–125).

2.3.3 Fibrinolytic therapy

Data on fibrinolysis in CS is limited, and the few studies have found no mortality benefit from thrombolytic therapy versus placebo (126). In a subgroup analysis of a STEMI trial called the GUSTO I (The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries), no mortality benefit was discovered between fibrinolytic strategies in CS, but PCI was associated with a lower mortality rate (127). Animal studies have suggested that the performance of thrombolytic therapies may be dependent on perfusion pressure and coronary blood flow (128), a reason why their benefit in CS patients may be limited. However, expert recommendations state that fibrinolysis may be considered in STEMI-related CS, if early invasive treatment is impossible in an adequate time (3,44).

2.3.4 Early revascularization

Current guidelines (41,87,109,129) recommend early revascularization in patients with ACS-related CS. The landmark SHOCK trial compared early revascularization and initial medical stabilization. It failed to prove survival benefit in the primary end-point at 30 days (130), but showed that early revascularization was associated with lower 6-month, and 1- and 6-year mortality (130,131). Another trial conducted in the same era, the (Swiss) Multicenter Trial of Angioplasty for Shock, (S)MASH, was unable to prove the survival benefit of early revascularization when compared to that of initial medical treatment, but significant problems arose with patient recruitment, since only 55 patients were randomized (132). A recent registry study from the USA compared conservative versus invasive management of patients with ACS-related CS and found lower in-hospital mortality in patients with invasive management (38% vs 60%) (133). A recent large registry study found that lack of PCI was independently associated with higher in-hospital mortality (5). In registry studies, an early revascularization strategy has been applied to 45% to 88% of the CS patients with increasing rates in recent years (4,5,10,28,60,63,65,134,135).

2.3.5 Time-to-revascularization

Time-to-revascularization has only been studied in STEMI-related CS patients. The FITT-STEMI trial showed the importance of prompt revascularization by investigating first medical contact to balloon time in patients with STEMI-related CS. In this study, every 10-minute treatment delay resulted in 3.31 additional deaths in 100 PCI-treated CS patients without out-of-hospital cardiac arrest (136). Another recent study examined first medical contact to device time, and found that only one third of patients achieved the target of 90 minutes, and that first medical contact to balloon time > 90 minutes versus ≤ 90 minutes was independently associated with in-hospital mortality (137). In addition, shorter symptom onset to balloon time (25,138) and shorter door to balloon time have been associated with better survival (138). Interestingly, in the SHOCK trial, the median time from shock to PCI was 5.3 hours, with no association between shock onset to balloon time and mortality (121).

2.3.6 Revascularization strategies

Complete revascularization, in which the treatment goal is to address both culprit and haemodynamically significant non-culprit lesions during early revascularization, has historically been the preferred strategy in patients with ACS-related CS and was recommended in the CS guidelines (3,41). Indeed, in stable patients with STEMI, treatment of culprit- and non-culprit vessels at the time of primary PCI has proven feasible, safe, and has been associated with better outcomes (139–141). In observational studies comparing multivessel- vs. culprit-vessel PCI strategy in CS patients, some studies have found multivessel PCI to be associated with better survival (142–144), whereas others have found no difference in outcome (121,145–148). A systematic meta-analysis showed higher short-term mortality in patients treated with multivessel PCI than with culprit lesion only PCI (149), while other meta-analyses found no difference in outcome (150).

The CULPRIT-SHOCK (Culprit Lesion Only PCI Versus Multivessel PCI in Cardiogenic Shock) trial randomized ACS-related CS patients with multivessel disease into two revascularization strategies: either PCI of the culprit lesion only, with the option of staged revascularization of non-culprit lesions, or immediate multivessel PCI (151). The strategy of PCI to the culprit lesion only was associated with lower risk of the composite end-point of all-cause mortality or of severe renal failure than was immediate multivessel PCI (151). A one year follow-up showed no mortality difference, but patients with PCI only of the culprit lesion needed more hospitalizations for heart failure and repeat revascularizations (152). Currently, ESC guidelines of myocardial revascularisation recommend culprit-lesion-only PCI as the default strategy

in patients with ACS-related CS. However, multivessel PCI may be considered in some patients, for instance, if difficulties arise in identifying the culprit lesion (87).

Another treatment option for early revascularization in CS is emergency coronary artery bypass grafting (CABG). Currently, the rate of urgent CABG in patients with STEMI is reportedly around 4% to 10% (5,61,65,153) and even up to 29% in NSTEMI patients (135). Overall, data concerning CABG in CS patients are scarce. In a sub-analysis of the SHOCK trial, no differences in mortality appeared between CABG and PCI treatment, despite the fact that CABG was more often performed in patients with a high risk profile and advanced multivessel disease, whereas patients with fewer comorbidities and a lower extent of coronary artery disease prevailed in the PCI arm (154). In the SHOCK trial registry, mortality was higher in patients with PCI treatment than with CABG, especially in those patients with multivessel disease (122). In a prospective study conducted between 1995 and 2004, mortality rates were numerically higher in the PCI group than in the CABG group (61). However, studies involving CABG and PCI treatment were not randomized, which means that selection bias should be considered; moreover, these studies were conducted back at the turn of the 21st century. Current ESC guidelines on revascularization suggest that CABG should be considered in CS patients with suitable anatomy, particularly if PCI is unfeasible (87). In addition, cardiologists and cardiac surgeons should make the decision about emergency CABG in collaboration, taking into account the patient's medical history, coronary anatomy, procedural risks, potential treatment-related delays, and also patient preferences (3,44).

2.3.7 Procedural characteristics of percutaneous coronary intervention

Coronary artery perfusion beyond point of occlusion can be assessed with Thrombolysis in Myocardial Infarction (TIMI) grade flow classification (Table 2) (155). In CS, unsuccessful revascularization of the IRA (TIMI < 3 post-PCI) is associated with poor prognosis (23–25,27–31,121,122). Currently, in ACS, the PCI procedure with balloon angioplasty and stent application is the recommended treatment method in ACS (87). In the SHOCK trial, only 34% of patients treated with PCI received stents, and coronary angiography was more often successful in stented than in non-stented patients (121). In addition, a study comparing outcomes between balloon angioplasty and stent placement showed a better outcome in CS patients with stenting (156).

In STEMI overall, the benefit of drug-eluting stents in comparison with that of bare metal stents has been evident in trials (157,158). In CS, no randomized trials of drug-eluting stents versus bare metal stents have appeared, but one propensity-score-matched study found drug-eluting stents

to be associated with improved clinical outcomes (159), and the other found no difference between effects of the two type of stents (160).

Table 2 TIMI grade flow descriptions (155).

TIMI grade flow	Description
TIMI 0 - no perfusion	no antegrade flow beyond the point of occlusion
TIMI 1 - penetration without perfusion	faint antegrade coronary flow beyond the occlusion with incomplete filling of the distal coronary bed
TIMI 2 - partial perfusion	delayed or sluggish antegrade flow with complete filling of the distal territory
TIMI 3 - complete perfusion	normal flow with complete filling of the distal territory

Current guidelines for myocardial revascularization recommend, in general, radial access over femoral access (87), but in CS, hypotension and vasoconstriction may complicate transradial catheterization; moreover, the need for larger bore access for support devices may favour the transfemoral approach (161). No randomized trials between transradial and transfemoral access in CS patients have emerged, but observational studies (162,163) and a meta-analysis showed better outcomes with radial access than with femoral access (164). Expert recommendations for CS propose preferential use of the radial approach (3,44), and ultrasound guidance may serve to facilitate vascular access (165).

In the setting of ACS-related CS, only sparse data are available on antithrombotic therapy. In general, dual antithrombotic therapy with aspirin and $P2Y_{12}$ inhibitors (clopidogrel, prasugrel, and ticagrelor) is the recommendation in all patients treated with PCI (87). A secondary analysis of the ISAR-SHOCK (Efficacy Study of LV Assist Device to Treat Patients With Cardiogenic Shock) registry compared clopidogrel and prasugrel in ACS-related CS, and found lower 30-day mortality in the prasugrel group (166). A sub analysis of the IABP-SHOCK II trial showed no difference in mortality between the clopidogrel and the ticagrelor or prasugrel groups, and no difference in bleeding complications (167).

Impaired gastrointestinal absorption in the context of myocardial infarction may make oral administration of antithrombotic medications problematic (166). Thus, intravenous antithrombotic medications such as glycoprotein IIb/IIIa inhibitors or the $P2Y_{12}$ inhibitor cangrelor may be considered. Observational studies have shown improvement in survival and a

higher procedure success with abciximab (168–170) and in one observational study, cangrelor was associated with TIMI improvement better than with oral $P2Y_{12}$ inhibitors, with a similar risk for bleeding (171). Overall, expert guidelines recommend dual antiplatelet therapy in patients with PCI treatment in CS, and if oral administration is impossible or there is doubt about absorption, an intravenous glycoprotein IIb/IIIa inhibitor or $P2Y_{12}$ inhibitor can be considered (3).

During PCI, an adjunctive anticoagulant is necessary. In choice of the anticoagulant, current expert recommendations are the same as for other types of ACS (3,44,87). If anticoagulation is required after PCI, the use of intravenous unfractionated heparin may be better than low-molecular weight heparin or fondaparinux, because of the high prevalence of acute kidney injury and acute liver injury (3).

2.3.8 SYNTAX scores

The SYNTAX score is an angiographic grading tool for the complexity of coronary artery disease calculated with a SYNTAX score algorithm, a computer program consisting of sequential and interactive self-guided questions (172). In this algorithm, each significant coronary artery lesion is evaluated separately, and the final SYNTAX score is the sum of the scores of each lesion. A lesion is defined as significant when it causes a ≥ 50% reduction in luminal diameter by visual assessment in vessels with minimal diameter of 1.5 mm. The SYNTAX score algorithm consists of 12 main questions, which characterise each lesion explicitly (Table 3). Each coronary segment is classified according to its estimated contribution to relative blood supply for the left ventricle and receives a weighting factor. For example, the weighting factor for an LM lesion is 5 or 6 depending on coronary artery dominance, whereas for an RCA lesion it is 0 or 1 (172).

Originally developed as a decision tool between PCI or CABG for patients with complex coronary artery disease (173), the SYNTAX has its baseline value calculated before any procedures to the coronary arteries. The prognostic value of baseline SYNTAX score was originally validated for long-term mortality in stable coronary artery disease (173,174), and has now proven its prognostic effect in large PCI all-comers' trials (175,176) as well as in STEMI (35–37,177) and in NSTEMI (178). One study evaluating baseline SYNTAX score in patients with STEMI-related CS found, for in-hospital mortality, 60% sensitivity and 59% specificity (179). In addition, a high baseline SYNTAX score has been associated with increased risk for CS (180), and the incidence of CS has been higher in patients with high baseline SYNTAX score (36,177).

Table 3 12 questions of the SYNTAX score algorithm

1.	Dominance
2.	Number of lesions
3.	Segments involved per lesion
4.	Total occlusions with subtotal occlusions
	a. Number of segments
	b. Age of total occlusions
	c. Blunt stumps
	d. Bridging collaterals
	e. First segment beyond occlusion visible by antegrade or retrograde filling
	f. Side branch involvement
5.	Trifurcation, number of segments diseased
6.	Bifurcation type and angulation
7.	Aorto-ostial lesion
8.	Severe tortuosity
9.	Lesion length > 20 mm
10.	Heavy calcification
11.	Thrombus
12.	Diffuse disease with number of segments

Adapted from the SYNTAX score algorithm. Features in blue are lesion characteristics, specified separately for each lesion (172).

Residual SYNTAX score is calculated after the PCI procedure (181) and can serve as an indicator of revascularization completeness. Residual SYNTAX score has been shown to have prognostic value in all-comers' PCI cohorts with complex coronary artery disease (182–189) as well as generally in ACS (181) and in STEMI (37–39). Complete revascularization is set at residual SYNTAX score 0 points, but in less than half the patients is complete revascularization achievable (39,181,185). This issue has led to the concept of reasonable incomplete revascularization, for which the residual SYNTAX score limit is set at 8 (39,182,185) or at 12 (188) points. In CS, residual SYNTAX scores await study.

2.3.9 Complications of percutaneous coronary intervention

Possible complications during the PCI procedure may include coronary artery dissection or perforation, side-branch occlusion, vascular complications, and arrhythmic complications such as ventricular fibrillation or tachycardia, or bradyarrhythmia due to sinus bradycardia or conduction block. In patients

with STEMI, incidence of any complication during LAD PCI has been 9% (33), with sustained ventricular arrhythmias witnessed in 4% of STEMI patients (190). One study reported procedural complications in patients with CS: the most common complication was coronary artery no-reflow or slow-flow in 6.1% of the patients, followed by arrhythmia requiring direct cardioversion in 4.4%, heart-block requiring temporary pacing in 3.9%, coronary dissection in 2.3%, side-branch occlusion in 0.9%, and coronary perforation in 0.4% (31).

2.4 Electrocardiography in cardiogenic shock

2.4.1 ST-segment elevation and depression

The ECG examines cardiac activity through electrical potentials measured from the surface of the body. In many pathologic circumstances, electrical potentials within the myocardium are altered, being reflected in the standard 12-lead ECG. ST-segment changes in CS have only been studied in the context of ACS, but in addition to myocardial ischaemia, ST-segment deviations are observable in other cardiac conditions such as acute pericarditis, myocarditis, LV hypertrophy, Brugada syndrome, or stress-induced cardiomyopathy (7,8). In an acute setting, reciprocal changes may help to differentiate STEMI from pericarditis or early repolarization changes (48,191). Diagnostic criteria for ST-segment deviations in this study are described in Table 4.

Table 4 Definitions of ST-segment deviations.

	Definition
STE ST-segment elevation	ST-segment elevation at the J point in two contiguous leads with cut-off points: ≥ 0.1 mV in all leads other than leads V2–V3, in which these cut-off points apply: ≥ 0.2 mV in men ≥ 40 years, ≥ 0.25 mV in men < 40 years or ≥ 0.15 mV in women
STDEP ST-segment depression	Horizontal or down-sloping ST-segment depression ≥ 0.05 mV in two contiguous leads
NSTED No ST-segment deviation or ST-segment impossible to analyse	ECGs with confounding ST-segment pattern: Left bundle branch bloc (LBBB), ventricular paced rhythm, ECGs with other changes (Q waves, T inversion without ST deviation, or a normal ECG.

Adapted from the Third Universal Definition of Myocardial Infarction (192).

Pathogenesis of STE has previously been examined closely. Acute ischaemia due to compromised blood supply to the myocardium alters the electrical properties of the myocardium, thus leading to repolarization abnormalities. In general, STE results from electrical changes associated with transmural ischaemia (Figure 3) (193). After coronary artery occlusion, the ischaemic myocardial cells consume all available oxygen within minutes. When oxygen is no longer available, oxidative phosphorylation comes to a complete halt. In the ischaemic heart, hydrolysis of adenosine triphosphate results in large amounts of phosphate, which pours out into the intracellular space. In order to maintain electrical neutrality, phosphate anions are accompanied by potassium, the major intracellular cation. This causes a large potassium efflux, which results in depolarization of the ischaemic myocardial cells (194). The depolarization of ischaemic myocardial cells causes an electrical gradient between the resting potentials of ischaemic and viable myocardium that allow the current to flow between the normally perfused and ischaemic regions of the heart. These injury currents are visible on the surface ECG as STE (193,195). In addition to the injury currents, a second theory explains STE as a difference in plateau potentials of the epicardium and endocardium, because ischaemia causes depression of the action potential plateau in the epicardium but not in the endocardium, resulting in a transmural voltage gradient (196).

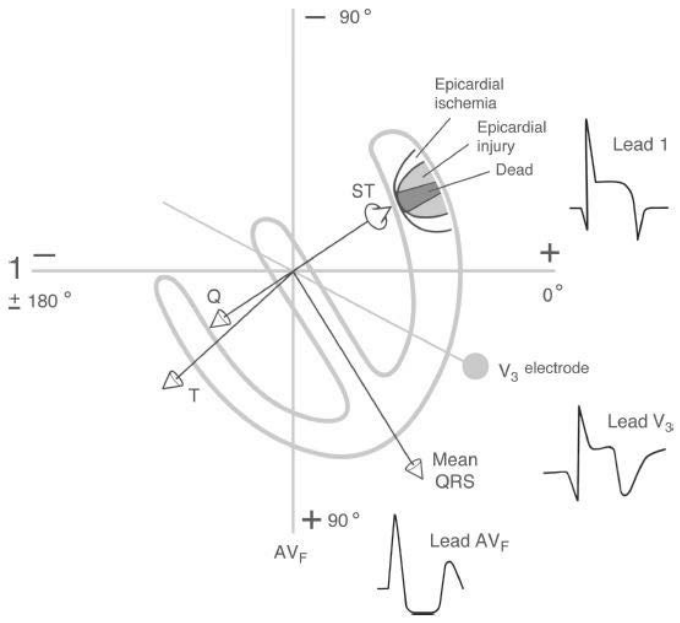


Figure 3 The development of ST-segment elevation. The mean spatial ST-vector is directed toward the area of predominant epicardial injury. Reproduced with the permission of Wiley (197).

Especially in STEMI, ECG patterns are well characterised. The ECG changes begin rapidly after total coronary artery occlusion, and without therapeutic intervention, these changes progress typically (198). The first findings are hyperacute T waves, following STE, abnormal Q waves, T-wave inversion, and finally, normalization of the ST segment (191,199,200). Because acute myocardial ischaemia results in dynamic changes in ECG pattern, serial ECG acquisition can provide critical information (48). The localisation of STE often reveals the culprit artery, since anteroseptal STE is associated with LAD occlusion, and inferior or lateral STE with LCX or RCA occlusion (201,202). In addition, the localisation of STE is associated with prognosis of ACS, with patients having anterior STE showing worse outcome than to those with inferior or lateral STE (203,204).

The pathophysiology of STDEP is more elusive. Traditionally, the view is that STDEP results from subendocardial ischaemia. In this theory, a layer of perfused myocardium separates the partially depolarized endocardium from the epicardial surface of the heart, which is reflected as STDEP (Figure 4) (205). STDEP is common in demand ischaemia, because the workload of the subendocardial myocytes of the left ventricle is greater than that of the myocytes of the epicardium, due to the unique anatomy of the left ventricle. Consequently, energy demands are highest in the endocardium, making the endocardium more prone to energy starvation than is the epicardium (197). Overall, STDEP and subendocardial ischaemia are not well defined in the current literature, because reproducing subendocardial ischaemia in animal models has proven difficult (206). In general, STDEP does not localize cardiac ischaemia (205). However, global ischaemia pattern, with STDEP > 1 mm in six leads, associated with STE in leads aVR or lead V1, is suggestive of widespread ischaemia resulting from multivessel disease or LM disease (48,207), and it has been associated with worse ACS outcome (208). This pattern has not been studied in CS patients, however.

In general, studies reporting ECG changes in CS are scarce. In the SHOCK trial, patients often had extremely abnormal ECG characteristics such as persistent STE, widespread STDEP, and a high incidence of conduction abnormalities (20). An association appeared between the total sum of STDEP of all leads and 1-year mortality in those randomized to initial medical stabilization, but not in those randomized to emergency revascularization (20). One study reported that a higher total ST sum of ST deviation was associated with CS development in ACS patients (209).

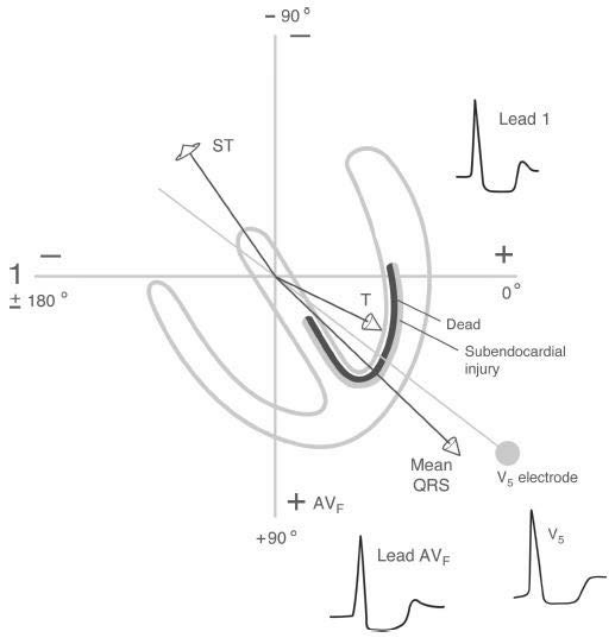


Figure 4 The development of ST-segment depression. The mean spatial ST-vector is directed away from subendocardial injury, causing STDEP. Reproduced with the permission of Wiley (197).

ST-segment patterns have only been addressed in studies investigating STEMI and NSTEMI, but not in patients with other CS aetiologies. CS incidence is higher among STEMI patients than among those with NSTEMI (6% to 12% vs. 2% to 4%) (1,62,65,135). Patients with NSTEMI are older, more often female, and have more comorbidities than do patients with STEMI (62,210,211). Short-term mortality rates in STEMI-related CS have been reported at 33% to 45% (1,62,212) in comparison to 34% to 41% in NSTEMI (1,62,135). Three studies reported NSTEMI patients to have higher mortality than STEMI in CS (60,62,210), while two studies found no mortality difference (11,211). A large registry study from the USA reported that in CS-related STEMI, mortality rates were highest when CS developed during the first 24 hours of hospitalisation, in comparison to CS at admission or after 24 hours of hospitalisation, while in NSTEMI, those patients with CS at admission had the highest short-term mortality rates (10).

2.4.2 Ventricular conduction disturbances

Under normal conditions, the action potential generated by the sinoatrial node spreads through the atria to the atrioventricular (AV) node, from where it continues to the ventricles through the bundle of His, bundle branches, and fascicles, and finally to the Purkinje fibres, which produce rapid and synchronous depolarization and contraction of ventricular cardiomyocytes. Left bundle branch block (LBBB) results from a conduction disturbance in the predivisional segment of the left bundle branch, or in both left anterior and posterior fascicles. This causes alteration of the normal sequence of activation in the myocardium, with the ECG showing a characteristic LBBB appearance. If the disturbance is only in the anterior or posterior fascicle, it leads to left anterior hemiblock (LAHB) or left posterior hemiblock (LPHB) (213). Correspondingly, right bundle branch block (RBBB) results from conduction disturbance in the right bundle branch. Unspecified intraventricular conduction delay (IVCD) refers to a situation in which QRS duration is prolonged, but the diagnostic definitions for any conduction block is unfulfilled. For definitions of each conduction disturbance see Table 5.

Table 5 Definitions used for of ventricular conduction blocks in this study.

Block type	Definition
LBBB	QRS duration ≥ 120 ms Tall R, broad or notched R waves in the lateral leads (I, V5-6) Deep S waves in the right precordial leads (V1-3) Absence of septal Q waves in the lateral leads (I, V5-6)
RBBB	QRS duration ≥ 120 ms Wide or notched R wave in leads V1 or V2 Slurred S wave of greater duration than R wave in leads I and V6
LAHB	Left axis deviation (-30° to -90°) qR pattern (small q, tall R) in the lateral limb leads I and aVL rS pattern (small r, deep S) in the inferior leads II, III, and aVF QRS width < 120 ms (in the absence of RBBB)
LPHB	Right axis deviation (90°-180°) rS pattern in leads I and aVL qR pattern in leads III and aVF QRS width < 120 ms (in the absence of RBBB)
IVCD	QRS ≥ 110 ms without bundle branch blocks and hemiblocks

Adapted from AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part III: intraventricular conduction disturbances (214).

In the general population, the prevalence of different ventricular conduction blocks is low, around 1% (215,216). Ventricular conduction blocks may be associated with various cardiac conditions such as ischaemic heart disease, cardiomyopathies, hypertension, or congenital heart disease (217,218). In CS, ischaemia (219), or overstretching of the conduction fibres due to ventricular wall stress (220,221), may damage the conduction network within the ventricles, resulting in slow impulse conduction through the cardiomyocytes, seen in ECG as intraventricular conduction disturbances. The term 'intraventricular conduction disturbance' comprises all abnormalities in intraventricular conduction that result in changes in the shape or duration, or both, of the QRS complex.

Ventricular conduction disturbances induced by ischaemia are often visible in the form of conduction blocks (222). Since the myocardium is less resistant to ischaemia than is the conduction system, occurrence of a bundle branch block may relate to extensive and on-going myocardial infarction (17,223). Appearance of a new RBBB may be explained by occlusion in the proximal section of the LAD before the septal branches, because the course of the right bundle branch goes through the anterior septum (224,225). More extensive injury is required to cause LBBB, as the left bundle branch is supplied usually by two of the three main coronary arteries: the septal branches of the LAD and the AV nodal branch, which is a distal branch of the RCA or less frequently a branch of the LCX (225). The structure of the left anterior fascicle is thin and long and is thus susceptible to ischaemia. It is supplied by septal branches of the LAD (226). In contrast, the left posterior fascicle is short and thick and better protected from ischaemia, as it has a double blood supply from the LAD and the posterior descending branch, which is usually a distal branch of the RCA (226,227) (Figure 5).

Ischaemia can also cause QRS complex prolongation, seen as IVCD. This kind of conduction disturbance is explained by injured myocardium, in which the areas of slowed ventricular activation and electrically inactive tissue cause increased duration of depolarization, resulting in QRS prolongation (222). In studies addressing slowed ventricular activation, the prolongation of depolarization is considered to be characteristic of a peri-ischaemic block (17,18). Due to the reversible mechanism, ischaemia-related QRS prolongation is often transient (17,18). In addition to conduction blocks and QRS prolongation, changes in the amplitude of QRS are common, i.e. the increase in amplitude of R waves and disappearance of S waves, which are explained by prolongation of electrical conduction in the Purkinje fibres in the ischaemic region (9). These kinds of changes may lead to a shift in the electrical axis, resulting in a hemiblock configuration (9,222,228). Overall, changes in the QRS pattern and duration are usually complimentary to ST-segment deviation and may reflect more severe ischaemia and progression of irreversible myocardial necrosis (9,229).

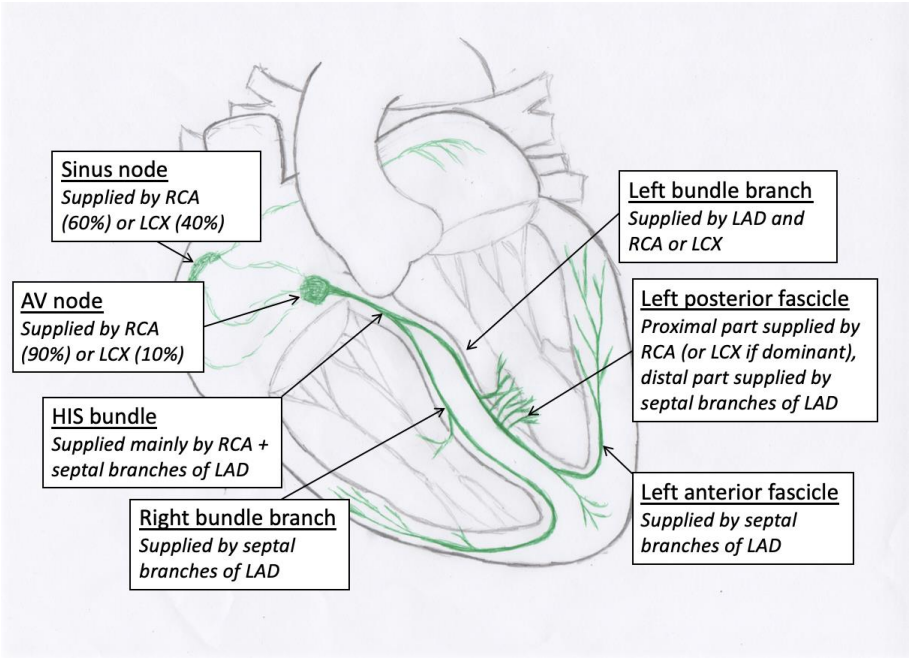


Figure 5 Arterial supply of the conduction system. AV = atrioventricular, LAD = left anterior descending artery, LCX = left circumflex artery, RCA = right coronary artery. Reproduced with permission of the illustrator (230).

In ACS patients with ventricular conduction disturbances, CS incidence is up to 19% (10,12–14) and higher than that reported in STEMI (1,62,65). One study found that, in patients with STEMI, RBBB was an independent predictor of CS development (209). RBBB and LBBB were more common in patients with anterior myocardial infarction than with other infarct locations (12,204), and RBBB was associated with LAD as the culprit artery and LBBB with RCA as the culprit artery (12). Three studies have reported the prevalence of ventricular conduction disturbances in CS patients, in whom RBBB was present in 13% to 20%, and LBBB in 2% to 10% (11,20,209). A small study of CS patients with LM as the culprit artery reported a prevalence of RBBB as high as 48% (21). Reversion of ventricular conduction blocks in acute ischaemia is common, and new-onset blocks are more likely to revert back to normal (231,232).

In ACS, ventricular conduction disturbances have been associated with worse outcome (11,12,14–16). Some studies have found higher mortality in general with ventricular conduction blocks, but no difference in survival between LBBB and RBBB (14), especially in long-term follow-up (15). In

GUSTO I trial patients, RBBB + LAHB showed the strongest association with mortality, followed by isolated RBBB. In addition, post-thrombolytic reversion of the bundle branch block was associated with better survival in 30 day follow-up (12). Another study had similar results, since it showed that RBBB was associated with poor outcome, and higher mortality was especially associated with new-onset RBBB in comparison with old RBBB, persistent RBBB in comparison with reversible RBBB, and bifascicular RBBB in comparison with isolated RBBB (16). Another study also reported that new-onset BBB was associated with worse outcome in comparison with old BBB (14). A more recent study reported that in-hospital mortality was highest among patients presenting with new or presumably new RBBB, followed by new or presumably new LBBB, old LBBB, and old RBBB (13).

Few studies have examined ventricular conduction disturbances in CS. In the SHOCK trial, prolonged QRS was associated with increased 1-year mortality in patients randomized to initial medical stabilization, but not in those randomized to emergency revascularization (20). In two studies of ACS-related CS, RBBB was associated with poor short- and long-term prognosis (11,21).

2.4.3 Heart rate and arrhythmias

In ACS patients, higher heart rate at admission has been associated with higher CS incidence (153,209) and with worse outcome (81,233). Previously, higher heart rate was associated with increased one-year mortality in the SHOCK trial patients (20) as well as in STEMI-related CS patients (234). An elevated heart rate slows the decrease in cardiac output, but it also raises myocardial oxygen consumption. In addition, myocardial perfusion time decreases (235). Heart rate elevation may be iatrogenic, since the most commonly chosen inotrope dobutamine causes tachycardia, which may contribute to haemodynamic compromise and may predispose to arrhythmias (236). As β-blockers are contraindicated in unstable patients (3,109), selective heart rate reduction may be better tolerated in patients with CS. Ivabradine is the only selective heart-rate-lowering agent that acts by inhibition of the $I_{(f)}$-channel in the sinus node, thus having no effect on haemodynamics or on myocardial contractility (237). In two small studies in CS patients, ivabradine was well tolerated and was also associated with short-term favourable outcomes (238,239), but use of ivabradine in patients with cardiogenic shock is experimental, and by far only recommended in stable heart failure (41).

In CS patients, the overall incidence of atrial fibrillation is 10% to 30%. In ACS, atrial fibrillation has been associated with worse outcome (240,241). In CS, several mechanisms expose patients to atrial fibrillation, notably increase in capillary wedge pressure and in left atrial pressure (242). One hypothesis is that, in CS, atrial fibrillation causes haemodynamic instability

resulting from loss of atrial contraction and of AV synchrony, from rapid ventricular rates, and from irregular RR interval; atrial fibrillation may thus lead to worsening symptoms and to worse clinical outcomes. (242). However, an IAPB-SHOCK II trial substudy found no difference in mortality between patients presenting with or without atrial fibrillation in 30-day and 1-year follow-up (243).

In ACS-related CS, ventricular tachycardias are common (242). Sustained ventricular tachycardias have been reported in 17% to 21% and ventricular fibrillation in 20% to 29% (153,234,244). Especially in CS, sustained ventricular tachycardias are prone to causing haemodynamic collapse, which is why immediate direct current cardioversion is recommended (242). Antiarrhythmic therapy and electrolyte balance correction should also be considered (245), taking into account the hypotensive likelihood of intravenous administration of amiodarone (246). If ventricular tachycardia is recurrent, catheter ablation may be indicated as a salvage procedure (242,247).

2.4.4 Atrioventricular conduction disturbances

The incidence of high-grade AV block in ACS has declined due to improved therapeutic interventions (248). In ACS-related CS, high-grade AV block and asystole develop in about 10% to 35% of all patients (30,153,209), with inferior infarctions resulting from proximal RCA occlusion being the main risk factor (249). In ACS-related CS, bradyarrhythmias are induced by either necrosis of the conduction system or by autonomic imbalance with vagal hyperactivity (242). In ACS patients, high-grade AV block is associated with higher mortality (248–250), but its significance as a prognostic marker in CS patients is unknown. For patients with severe life-threatening bradyarrhythmias, emergency temporary transvenous pacing is necessary, especially if the arrhythmias do not resolve within a few minutes after reperfusion (109,242,251).

3 AIMS OF THIS STUDY

This study investigated electrocardiographic and angiographic features in patients with CS. First, we studied the prevalence of various parameters in standard 12-lead ECG and examined their effect on survival. Secondly, we studied angiographic features, including the extent of coronary artery disease, procedural success, and baseline and residual SYNTAX scores, and assessed their prognostic significance in CS.

In more detail, the aims were:

1. To describe the prevalence of different ST-segment deviations and their association with CS aetiology, clinical findings, and 90-day mortality in CS patients with various aetiologies. (I)

2. To assess the prevalence, temporal evolution, and the impact on survival of ventricular conduction blocks in patients with ACS-related CS. (II)

3. To describe the baseline and residual SYNTAX score values in STEMI-related CS patients and to evaluate their added prognostic value over baseline covariates and clinical risk scores. (III)

4. To analyse the angiographic features, the effect of procedural timing, and the success of percutaneous coronary intervention in patients with ACS-related CS. (IV)

4 SUBJECTS AND METHODS

4.1 The CardShock Study

This is an observational study based primarily on the CardShock study, a prospective, observational, multinational study of CS. The CardShock study was coordinated by the Heart Failure Study Group of Helsinki University Hospital and was conducted in eight countries (Czech Republique, Denmark, Finland, Greece, Italy, Poland, Portugal, and Spain) and in nine centres across Europe. The recruitment period was from October 2010 to December 2012.

The CardShock study enrolled consecutive patients aged over 18 years within six hours after detection of CS. The criteria for shock were SBP < 90 mmHg for 30 minutes despite accurate fluid therapy, or a need for vasoactive therapy and ≥ 1 signs of inadequate organ perfusion: confusion or altered mental status, cool extremities, oliguria < 0.5 ml/kg/h for the previous 6 h, or blood lactate > 2 mmol/l. Patients were excluded for ongoing haemodynamically significant arrhythmia and shock after cardiac or non-cardiac surgery.

Patients' demographic characteristic and comprehensive medical history were collected, with clinical signs and laboratory measurements registered at baseline and every 6 to 24 hours. Creatinine, C-reactive protein (CRP), high-sensitive troponin T (hs-TnT, Elecsys, Roche Diagnostics, Basel, Switzerland), and N-terminal pro-natriuretic peptide (NT-proBNP, Elecsys, Roche Diagnostics) were measured at a central laboratory (ISLAB, Kuopio, Finland). Arterial blood lactate and pH were analysed locally. Estimated glomerular filtration rate (eGFR) was calculated from creatinine values by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation. ECGs were recorded at baseline and at day 3. The echocardiogram was performed per protocol at study entry. Patients were treated according to local practise and treatments, and procedures were registered and detailed information from coronary angiography was collected.

The CardShock study was accepted by local ethics committees at the participating centres except for Denmark, Copenhagen. Approval from the Danish Ethics committee was unnecessary, as the Danish law does not require ethical approval if the study utilizes information from existing registries, but approval of the study came from the Danish Protection Agency. The CardShock study was conducted in accordance with the Declaration of Helsinki. All patients or their next of kin provided informed consent. The primary endpoint was 90-day mortality in Studies I, III, and IV and was one-year mortality in Study III; three patients were lost to follow-up.

The descriptions of the study population and predictors of in-hospital mortality were published previously (85). Briefly, the main aetiology of CS was

ACS (81%). Other causes of CS were exacerbation of chronic heart failure, valvular dysfunction, stress-induced cardiomyopathy, and myocarditis. In comparison of patients with ACS and non-ACS aetiology, ACS patients were older (68 ± 11 years vs. 62 ± 15 years) and more often were men (88% vs. 57%). In-hospital mortality was 40% in ACS and 24% in non-ACS patients. A risk prediction model called the CardShock risk score we developed from the clinical and biological parameters incorporating seven variables with a maximum of nine points (Table 6). The CardShock risk score performed well in prediction of in-hospital mortality in the CardShock cohort with an area under the curve (AUC) of 0.85 (95% CI 0.80 to 0.90) (85).

Table 6 The CardShock risk score (85)

Variables	Score
Age >75 years	1
Confusion at presentation	1
Previous myocardial infarction or CABG	1
ACS aetiology	1
LVEF <40%	1
Blood lactate	
<2 mmol/L	0
2-4 mmol/L	1
>4 mmol/L	2
$eGFR_{CKD-EPI}$	
>60 mL/min/1.73m^2	0
30-60 mL/min/1.73m^2	1
<30 mL/min/1.73m^2	2
Maximum	**9**

Abbreviations: ACS = acute coronary syndrome, CABG = coronary artery bypass graft surgery, $eGFR_{CKD-EPI}$ = estimated glomerular filtration rate by the Chronic Kidney Disease Epidemiology Collaboration formula, LVEF = left ventricular ejection fraction. Reproduced with the permission of Wiley.

4.2 Study population and study outlines

4.2.1 Study I

Study I included 196 CardShock patients with a baseline ECG available. A subgroup analysis involved patients with ACS-related CS. Topics of the study were the prevalence of ST-segment deviations in baseline ECG and their association with CS aetiology and mortality.

The baseline ECG analysis utilised a custom-made non-commercial software engineered for ECG analysis at the University of Helsinki. The examiner defined electronically for the analysis program the baseline of the ECG at the level of the PQ interval and all key points in each ECG: the start and end points of the P wave, each component of the QRS-complex individually, the J point and the ST-segment at 0.04 and 0.08 s after the J point, and the start, peak, and end points of the T-wave. The software calculated time intervals and voltage differences between the specified points and the ECG baseline.

ST-segment deviations were defined according to the third universal definition of myocardial infarction (192). ECGs with LBBB or ventricular paced rhythm were excluded from ST-segment analysis. Patients were divided into three groups according to their ST-segment pattern: ST-segment elevation (STE), ST-segment depression (STDEP), and no ST-segment deviation or ST-segment impossible to analyse (NSTD). Those patients with both STE and STDEP were included in the STE group. STE localisation was assessed in patients with STE.

4.2.2 Study II

Study II included 199 patients with ACS-related CS from two different cohorts. A larger cohort of 155 were CardShock patients with ACS aetiology and baseline ECG available. A second cohort of 44 included patients from another prospective observational study of ACS-related CS conducted at the Brno University Hospital in the Czech Republic (58). The enrolment period for the second cohort was between January 2006 and June 2011. The inclusion criteria for the Brno University CS study were similar those of the CardShock study, and the exclusion criteria were ongoing resuscitation since the time of admission without return of spontaneous circulation, non-confirmation of ACS as the cause of CS, non-acquisition of the study consent form, malignancy, and inflammatory disease or connective tissue disease. Originally, the Brno University CS study included 80 patients, but only those 44 with baseline ECG available we included in Study II.

The baseline and day-3 ECGs were analysed by three independent researchers. QRS duration was analysed with a custom-made non-commercial software engineered for ECG analysis at the University of Helsinki as described in Study I. QRS configuration and rhythm we analysed visually. LBBB and RBBB we defined by standard criteria (252). LAHB we defined as QRS axis between -45 and -90°, qR/R in leads I and aVL, rS in leads II, III, and aVF, and QRS <120 ms if without concomitant RBBB. LPHB was defined as QRS axis > 90°, qR complex in lead III and rS complex in lead I, and QRS < 120 ms, if without concomitant RBBB. IVCD was identified as QRS duration ≥ 110 ms not fulfiling the criteria of either bundle branch block or hemiblock (253,254). Temporal evolution of conduction pattern was assessed from baseline to day 3. Investigation of the pre-existence of the block required a retrospective search of the previous ECGs of those patients with a ventricular conduction block in the baseline ECG from the three largest study centres (Helsinki, Brno, Barcelona).

4.2.3. Study III

Study III included CardShock patients from the two largest CardShock centres (Helsinki and Barcelona). The 61 STEMI patients included those treated with primary or rescue PCI and those with angiograms available. STEMI was defined according to the third universal definition of myocardial infarction (192). SYNTAX scores were calculated from the angiograms by means of the SYNTAX score algorithm (172) by two investigators blinded to patient data.

The SYNTAX scores were calculated at three points. Baseline SYNTAX score 1 was measured from the initial diagnostic angiogram, and baseline SYNTAX score 2 was measured after wiring or thrombectomy. If TIMI flow did not improve, or the anatomy of the IRA could not be assessed, baseline SYNTAX score 2 was the same as Baseline SYNTAX score 1. The residual SYNTAX score was calculated after completion of primary PCI. If staged angiograms were performed during the hospital stay, residual SYNTAX score was measured after all PCI procedures.

4.2.4 Study IV

Study IV included 158 CardShock patients with ACS-related CS with angiographic data available. The treating physician analysed the angiographic images. The characteristics of coronary artery disease, including the extent of coronary artery disease and the culprit artery, underwent analysis. Procedural characteristics examined included type and number of stents, symptom-to-balloon time, success of revascularization, and complications during the PCI procedure.

Table 7 summarizes specific inclusion criteria and the number of included and excluded patients in each study.

Table 7 Number of included and excluded patients in each Study

	Study I	Study II	Study III	Study IV
Inclusion criteria	▪ Any CS cause ▪ Baseline ECG available	▪ CS cause: ACS ▪ Baseline ECG available	▪ CS cause: STEMI ▪ patients from Helsinki or Barcelona ▪ Primary or rescue PCI ▪ No previous CABG ▪ Angiographic data available	▪ CS cause: ACS ▪ Angiographic data available
Card Shock patients included, n	196	155	61	158
Excluded, total n	23	64	158	61
Cause of exclusion, n	No baseline ECG, 21	Other CS aetiology, 42	Patients from a centre other than Helsinki or Barcelona, 95	CS aetiology other than ACS, 42
	Idioventricular rhythm, 2	No baseline ECG, 16	CS aetiology other than STEMI, 42	No angiography performed, 10
		Only ventricular paced complexes or idioventricular rhythm, 6	No primary or rescue PCI, 14	No data on angiography, 6
			Previous CABG, 3	Lost to follow-up, 3
			Angiography unavailable, 4	
Brno patients included		44		
Excluded		40		
Cause of exclusion		No baseline ECG, 40		

Abbreviations: ACS = acute coronary syndrome, CABG = coronary artery bypass graft surgery, ECG = electrocardiogram, CS = cardiogenic shock, PCI = percutaneous coronary intervention, STEMI = ST-segment elevation myocardial infarction

4.3 Statistical Methods

Continuous results are presented as means and standard deviations (SD) or medians and interquartile ranges (IQR) and categorical variables as counts (percentages). Continuous variables were analysed with a T-test, Mann–Whitney U test, or Kruskal–Wallis test, as appropriate. Categorical variables were analysed with Chi-square test or Fisher's exact test.

The Kaplan–Meier method served to generate survival curves, and log-rank test to assess differences in survival. Univariable and multivariable Cox regression analyses for the risk of 90-day death were conducted. Univariable p-values were calculated for the control variables, and significant associates were included in the multivariable analysis. The final Cox regression models were formed applying stepwise selection.

In Study III, the predictive power of SYNTAX scores was assessed by use of receiver operating characteristic (ROC) curves. The interobserver variability (tertial partitioning) for the SS examiners was calculated in 48 independently analysed angiograms with Cohen's Kappa statistics.

A two-tailed p-value of < 0.05 was considered statistically significant. The confidence intervals (CIs) were calculated at the 95% significance level. In Studies I-III, the statistical analyses were performed using IBM SPSS Statistics for Windows, version 21 or 24 (IBM Corp., Armonk, NY, USA). In Study IV, the analyses were performed using R statistical software version 3.4.3 or above (The "R" Foundation for Statistical Computing, Vienna, Austria).

5 RESULTS

5.1 ST-segment deviations in cardiogenic shock (I)

5.1.1 Prevalence and association with ACS aetiology

Study I included 196 CardShock patients with baseline ECG available. Mean age was 66 ± 12 years old, and 74% men.

ST-segment deviations were observable in 157 patients (80%). More than half the patients had STE and 29% had STDEP. The remaining 20% had no ST-segment deviation, or the ST-segments were impossible to analyse (NSTD) (Figure 6A). No differences in age or gender emerged across study groups. STE patients had fewer comorbidities than in the other two groups, but they were more often smokers (Table 8).

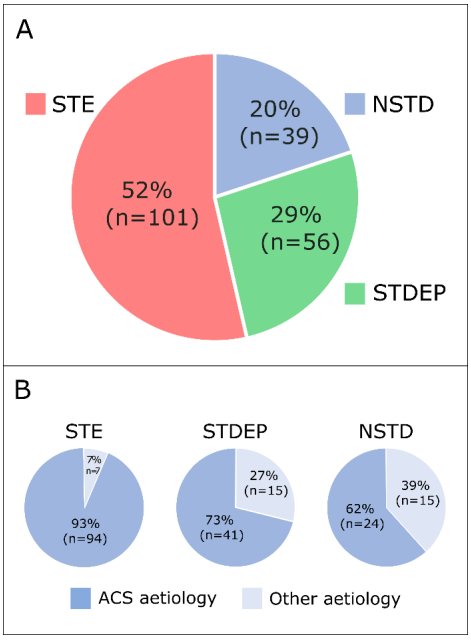


Figure 6 A) Prevalence of ST-segment deviations. B) ACS aetiology in patients with different baseline ECG ST-segment patterns. Abbreviations: NSTD = No ST-segment deviation or ST-segment impossible to analyse, STE = ST-segment elevation, STDEP = ST-segment depression. Reproduced with publishers permission from Study I (255).

Table 8 Baseline characteristics of Study I patients

	STE 101	STDEP 56	NSTD 39	p
Age, years	66 ± 12	69 ± 13	65 ± 12	0.16
Male gender (%)	76 (75)	38 (68)	31 (79)	0.41
Coronary artery disease (%)	28 (28)	22 (39)	18 (46)	0.04
Previous myocardial infarction (%)	24 (24)	14 (25)	10 (26)	0.97
Previous CABG (%)	5 (5)	4 (7)	3 (8)	0.76
Chronic heart failure (%)	10 (10)	14 (25)	8 (21)	0.04
Diabetes (%)	30 (30)	15 (27)	12 (31)	0.90
Hypertension (%)	61 (60)	33 (59)	23 (59)	0.98
Hypercholesterolemia (%)	49 (49)	25 (45)	18 (46)	0.89
Smoking (%)	48 (48)	18 (32)	13 (33)	0.03
Atrial fibrillation (%)	8 (8)	11 (20)	9 (23)	0.03
SBP, mmHg	78 ± 16	76 ± 12	80 ± 12	0.29
LVEF, %	35 ± 14	32 ± 15	32 ± 14	0.35
eGFR, ml/min/1.73m^2	60 (42-86)	62 (36-86)	67 (43-95)	0.71
Lactate, mmol/l	3 (2-6)	3 (1-5)	3 (2-6)	0.11
Hs-TnT, ng/l	3803 (1366-8849)	1132 (255-2761)	407 (115-2096)	0.02
NT-proBNP, ng/L	1611 (266-7649)	6020 (731-15754)	3160 (1501-7619)	0.15

Data presented as counts (percentages), means ± SD or medians (IQR). Abbreviations: ACS = acute coronary syndrome, CABG = coronary artery bypass grafting, eGFR= estimated glomerular filtration rate, hs-TnT = high-sensitive troponin T, LVEF = left ventricular ejection fraction, NSTD = No ST-segment deviation or ST-segment impossible to analyse, NT-proBNP = N-terminal pro-natriuretic peptide, SBP = systolic blood pressure, STE = ST-segment elevation, STDEP = ST-segment depression

The most common CS aetiology was ACS in 159 (81%) patients. ACS aetiology was more common in the STE group than the STDEP or the NSTD groups (93% vs. 73% and 62%; both $p < 0.01$, Figure 6B). Other aetiologies of CS are described in Table 9.

Table 9 Aetiologies of cardiogenic shock

	STE 101	STDEP 56	NSTD 39
ACS (%)	94 (93)	41 (73)	24 (62)
Exacerbation of chronic heart failure (%)	4 (4.0)	6 (11)	11 (28)
Valvular stenosis (%)	1 (1.0)	4 (7.1)	0 (0)
Valvular regurgitation (%)	1 (1.0)	2 (3.6)	0 (0)
Stress-induced cardiomyopathy (%)	0 (0)	1 (1.8)	3 (7.7)
Myocarditis (%)	1 (1.0)	2 (3.6)	1 (2.6)

Data presented as counts (percentages). Abbreviations: ACS = acute coronary syndrome, NSTD = No ST-segment deviation or ST-segment impossible to analyse, STE = ST-segment elevation, STDEP = ST-segment depression

5.1.2 Association of ST-segment deviations and mortality

During 90-day follow-up, 80 (41%) patients died. Mortality rates were similar between patients with different ST-segment patterns: in STE 47 (47%), in STDEP 20 (36%) and in NSTD 13 (33%) (p = 0.15, Figure 7A). Among the STE group, patients with anterior STE had a higher 90-day mortality rate than did patients with inferior STE (29 (56%) vs. 10 (28%); p = 0.01, Figure 7B).

In multivariable mortality analysis, STE was associated with worse outcome (HR 1.74, 95% CI 1.07 to 2.84; p = 0.03) when adjusted with significant covariates (age, history of coronary artery disease, SBP, lactate, and LVEF). Neither STDEP nor NSTD was associated with outcome in multivariable mortality analysis (Table 10A).

Patients with ACS tended to have higher mortality than did patients with other CS aetiologies (69 (43%) vs. 11 (30%); p = 0.09).

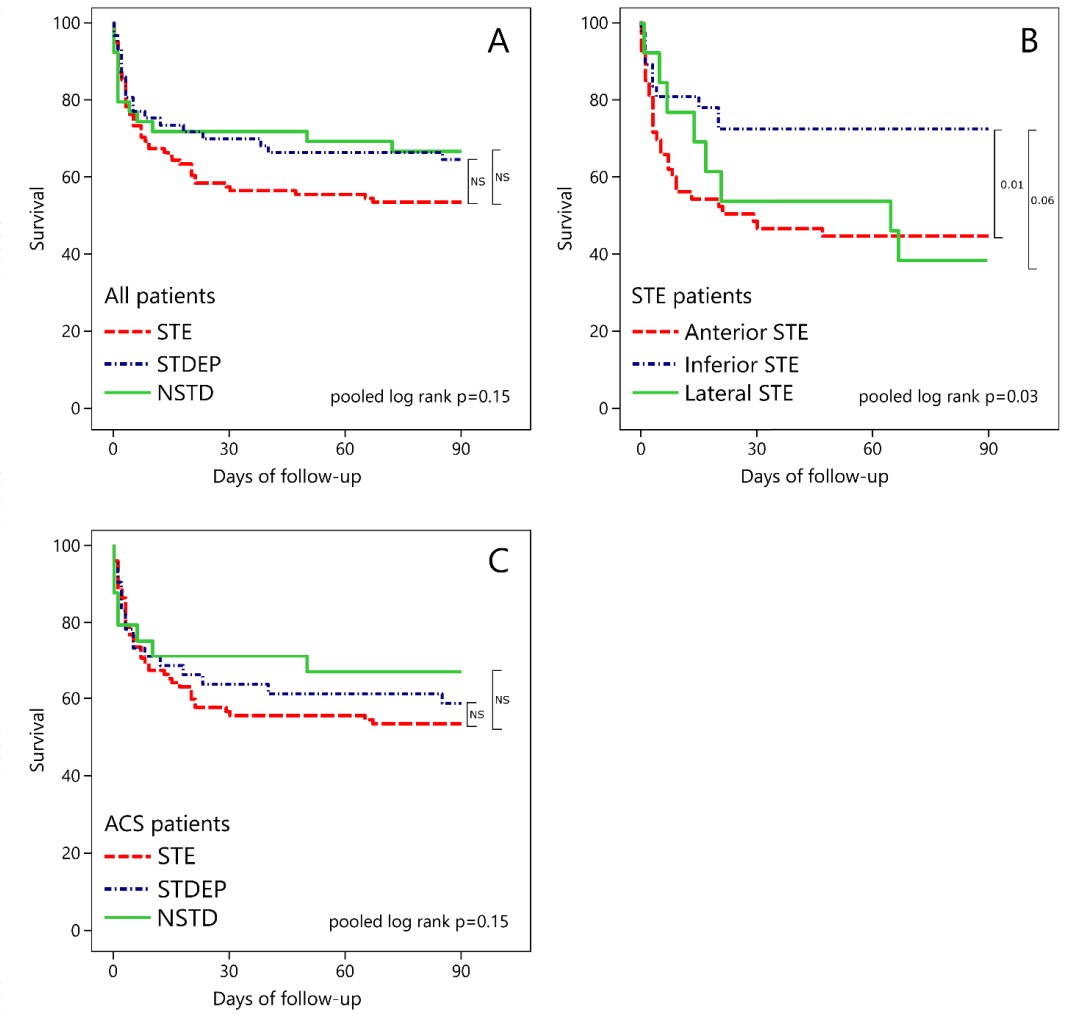


Figure 7 Kaplan–Meier 90-day survival curves (A) in all the study patients with the ST-segment patterns studied, (B) in STE patients with different STE locations, (C) in the ACS subgroup with the ST-segment patterns studied. Abbreviations: ACS = acute coronary syndrome, NSTD = No ST-segment deviation or ST-segment impossible to analyse, STE = ST-segment elevation, STDEP = ST-segment depression. Reproduced with publishers permission from Study I (255).

Table 10 Multivariable 90-day mortality analyses

	A: All patients HR (95% CI)	p	B: ACS subgroup HR (95% CI)	p
STE	1.74 (1.07 to 2.84)	0.03	1.55 (0.88 to 2.73)	0.13
STDEP	0.58 (0.33 to 1.02)	0.06	0.69 (0.37 to 1.29)	0.24
NSTD	0.81 (0.43 to 1.53)	0.52	0.79 (0.37 to 1.73)	0.56

Multivariable model adjusted for age, history of coronary artery disease, systolic blood pressure, lactate and left ventricular ejection fraction. Abbreviations: NSTD = No ST-segment deviation or ST-segment impossible to analyse, STE = ST-segment elevation, STDEP = ST-segment depression

5.1.3 ACS subgroup analysis

The ACS subgroup comprised of 159 patients. Among these patients, almost everyone underwent coronary angiography (94%) and PCI was performed in the vast majority (STE 92%, STDEP 87% and NSTD 86%; p = 0.48). STE patients less often had three-vessel disease than did the STDEP patients (24% vs. 42%; p = 0.04) (Table 11).

In the ACS subgroup, during the 90-day follow up, 69 (43%) patients died: in STE group 44 (47%), in STDEP 17 (42%) and in NSTD 8 (33 %) (p = 0.31) (Figure 7C) ST-segment patterns did not associate with outcome in multivariable mortality analysis (Table 10B).

Table 11 Angiographic features in the ACS subgroup

ACS Subgroup, 159	STE, 94	STDEP, 41	NSTD, 24	p
Coronary angiography performed (%)	91 (97)	38 (93)	21 (88)	0.22
Three-vessel disease (%)	22 (24*)	16 (42*)	7 (35*)	0.12
LM stenosis (%)	17 (19*)	9 (24*)	1 (5*)	0.15
PCI (%)	84 (92*)	33 (87*)	18 (86*)	0.51
TIMI 3 post-PCI (%)	59 (69*)	24 (75*)	15 (83*)	0.43

Data presented as counts (percentages). * Percentages in patients with coronary angiography performed. Abbreviations: ACS = acute coronary syndrome, LM = left main, TIMI = Thrombolysis in Myocardial Infarction

5.2 Ventricular conduction blocks in cardiogenic shock (II)

5.2.1 Prevalence of ventricular conduction blocks in baseline ECG

Study II included 199 ACS-related CS patients, of whom 155 patients were from the CardShock cohort and 44 from the Brno University CS study. Mean age was 66 ± 11 years, and 75% were men.

Ventricular conduction block was present in half of the patients; 8 had LBBB, and 10 had isolated RBBB. Concomitant RBBB and hemiblock was present in 18 patients (8 with RBBB + LAHB, and 8 with RBBB + LPHB). An isolated hemiblock occurred in 32 patients (25 with LAHB and 7 with LPHB) and IVCD in 32 (Figure 8). In 72 patients from Helsinki, Barcelona and Brno, previous ECGs were sought for retrospectively, and the previous ECG was found in 30 (42%).

Overall, patients with ventricular conduction block were older and had lower LVEF than patients with normal ventricular conduction (Table 12).

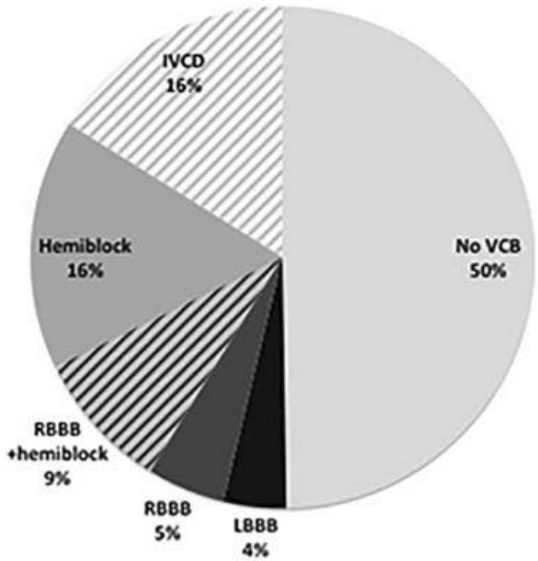


Figure 8 Prevalence of ventricular conduction blocks in ACS-related CS. Abbreviations: IVCD = unspecified intraventricular conduction delay, LBBB = left bundle branch block, RBBB = right bundle branch block, VCB = ventricular conduction block. Reproduced with publishers permission from Study II (256).

Table 12 Baseline characteristic of Study II patients.

	No VCB (n=99)	Any VCB (n=100)	LBBB (n=8)	RBBB (n=10)	RBBB + hemiblock (n=18)	Hemiblock (n=32)	IVCD (n=32)	p
Age, years	65 ± 11	69 ± 11*	75 ± 6*	72 ± 11	65 ± 12	70 ± 12*	67 ± 11	0.010
Men (%)	73 (74)	77 (77)	5 (63)	6 (60)	17 (94)	22 (69)	27 (84)	0.67
Diabetes mellitus (%)	27 (27)	39 (39)	5 (63)*	5 (50)	4 (22)	11 (34)	14 (44)	0.13
Coronary artery disease (%)	28 (28)	34 (34)	5 (63)*	3 (20)	6 (33)	7 (22)	13 (41)	0.24
Previous myocardial infarction (%)	23 (23)	22 (22)	4 (50)	2 (20)	4 (22)	5 (16)	7 (22)	0.49
Chronic heart failure (%)	6 (8)	8 (10)	2 (40)*	1 (17)	2 (14)	1 (3)	2 (7)	0.16
SBP, mmHg	80 (70–90)	80 (70–89)	85 (64–114)	78 (60–108)	80 (70–88)	80 (74–85)	80 (70–86)	0.94
Heart rate, BPM	87 (68–110)	93 (73–110)	89 (59–116)	92 (68–110)	87 (54–102)	99 (82–111)	91 (75–110)	0.85
LVEF, %	38 ± 14	33 ± 14*	26 ± 16	47± 15	30± 12	31 ± 14	34 ± 13	0.006
Lactate, mmol/L	2.5 (1.5–5.1)	3.3 (2.2–7.0)*	3.4 (3.1–3.7)	8.5 (4.2–13.3)*	2.7 (1.9–7.6)	4.1 (2.6–7.6)*	2.4 (1.6–4.9)	0.002
eGFR, ml/min/1.73 m^2	67 ± 29	57 ± 27*	50 ± 20	49 ± 24	62 ± 24	53 ± 24	63 ± 32	0.073
Peak hs-TnT, ng/L	5801 (3677–12628)	9293 (2224–22356)	1747 (763–27762)	423 (31–15503)	16963 (3656–43742)	16547 (6407–29879)	4763 (1912–11913)	0.015
Peak NT-ProBNP, ng/L	4544 (2013–9212)	9053 (3831–23651)*	18362 (7222–25733)	8033 (199–14711)	7200 (3775–12214)	17256 (4826–30617)*	6164 (2109–16547)	0.002
Three-vessel disease	35 (37)	26 (29)	4 (67)	3 (43)	4 (24)	9 (29)	6 (21)	0.23
LM stenosis (%)	9 (10)	22 (24)*	1 (17)	0 (0)	4 (24)	11 (34)*	6 (21)	0.023
TIMI 3 post-PCI (%)	67 (80)	57 (67)	5 (83)	6 (75)	12 (71)	19 (66)	15 (60)	0.38

Data presented as counts (percentages), means ± SD or medians (IQR).
*p < 0.05 when compared to patients with no ventricular conduction block (VCB).
Abbreviations: BMP = beats per minute, eGFR= estimated glomerular filtration rate, hs-TnT = high-sensitive troponin T, IVCD = unspecified intraventricular conduction delay, LBBB = left bundle branch block, LM = left main , LVEF = left ventricular ejection fraction, NT-proBNP = N-terminal pro-natriuretic peptide, PCI = percutaneous coronary intervention, RBBB = right bundle branch block, SBP = systolic blood pressure, TIMI = Thrombolysis in Myocardial Infarction, VCB = ventricular conduction block

5.2.2 Temporal evolution of ventricular conduction blocks

Temporal evolution of ventricular conduction blocks was assessed on day 3. Within the first three days, 32 (16%) patients died and were excluded from this analysis. Of the patients alive on day 3, 134 (80%) patients had ECG recorded.

Sixty (45%) patients had no conduction block either at baseline or at day-3 ECG (= no block). Persistent block was present in 33 (25%) (the same type of block in baseline and in day-3 ECG). Transient block appeared in 26 (19%) (the block present at baseline had disappeared at day 3). In 10 patients, the block present in baseline ECG had changed to another type of block, and 5 patients without a block in baseline ECG had a newly appearing block in day 3 ECG (Table 13).

Table 13 Temporal evolution from baseline to day 3 of the ventricular conduction blocks (VCB).

	No block	Block stayed	Block disappeared = transient block	Block changed	Block appeared
No VCB (%)	60 (92)	0	0	0	5 (8)
LBBB (%)	0	5 (83)	0	1 (17)	0
RBBB (%)	0	5 (83)	1 (17)	0	0
RBBB+hemiblock (%)	0	6 (38)	6 (38)	4 (25)	0
Hemiblock (%)	0	10 (56)	7 (39)	1 (6)	0
IVCD (%)	0	7 (30)	12 (52)	4 (17)	0
Total (%)	60 (45)	33 (25)	26 (19)	10 (8)	5 (4)

Data presented as counts (percentages). Abbreviations: IVCD = unspecified intraventricular conduction delay, LBBB = left bundle branch block, RBBB = right bundle branch block, VCB = ventricular conduction block

5.2.3 Association of ventricular conduction blocks and mortality

Patients with any ventricular conduction block had two-fold higher mortality than did patients with normal ventricular conduction (68% vs. 32%; $p < 0.001$, Figure 9).

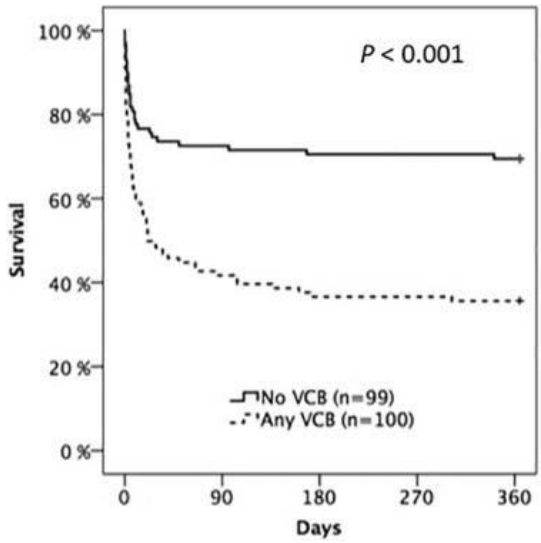


Figure 9 One-year Kaplan Meier curve in patients with any ventricular conduction block (VCB) or with normal ventricular conduction. Reproduced with publishers permission from Study II (256).

Adjusted mortality analysis used two multivariable models. The first multivariable model included the following significant baseline covariates: age, gender, history of hyperlipidaemia, chronic obstructive pulmonary disease, previous PCI or CABG, SBP, LVEF, and eGFR. The second multivariable model included angiographic findings and it included three-vessel disease, infarct-related artery, and TIMI 3 post-PCI.

Any ventricular conduction block was associated with one-year mortality when adjusted with baseline covariates (HR 2.0, 95% CI 1.2 to 3.2; $p = 0.004$) or with coronary angiographic findings (HR 2.0, 95% CI 1.2 to 3.2; $p = 0.006$). When each ventricular conduction block was studied separately, each ventricular conduction block at least tended to associate with one-year mortality ($p < 0.10$) in the two multivariable models, except for IVCD when adjusted for previously described coronary angiogram findings (Figure 10).

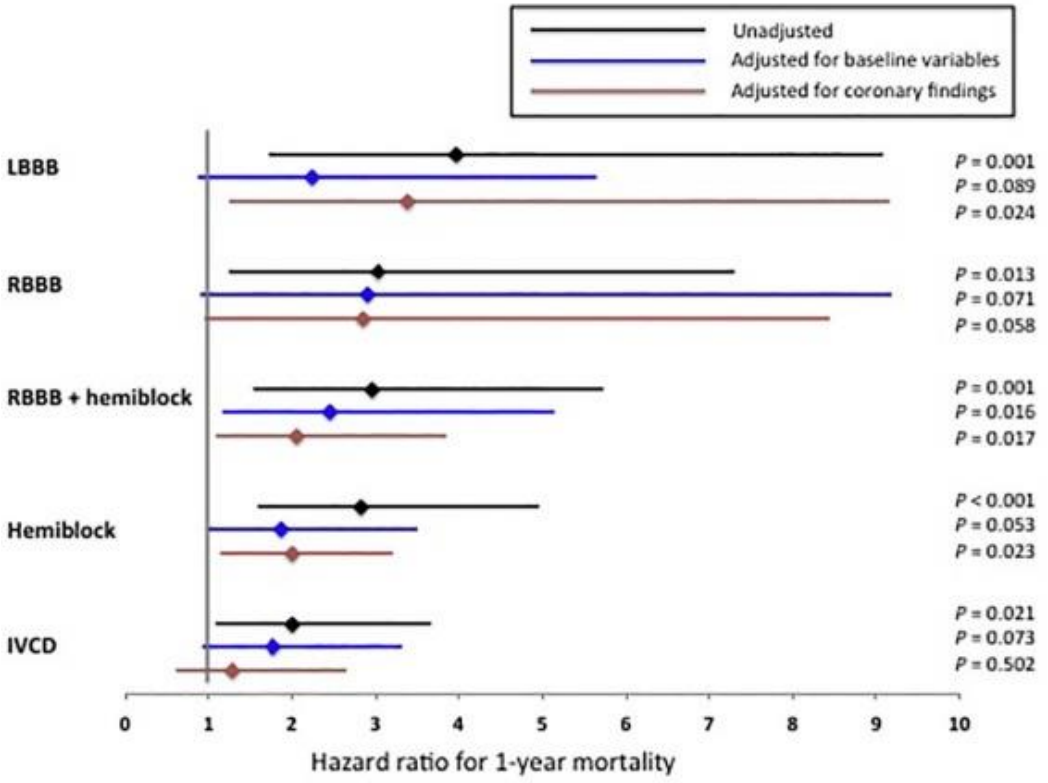


Figure 10 Forest box plot for one-year mortality in patients with different ventricular conduction blocks. Abbreviations: IVCD = unspecified intraventricular conduction delay, LBBB = left bundle branch block, RBBB = right bundle branch block, VCB = ventricular conduction block. Reproduced with publishers permission from Study II (256).

Regarding temporal evolution of the blocks, one-year mortality was highest (18, 69%) in patients with transient block (Figure 11). In multivariable analysis, transient block was associated with one-year mortality when adjusted with baseline covariates (HR 4.4, 95% CI 2.0 to 9.6; p < 0.001) or with coronary angiography findings (HR 4.6, 95% CI 2.0 to 10.6; p < 0.001).

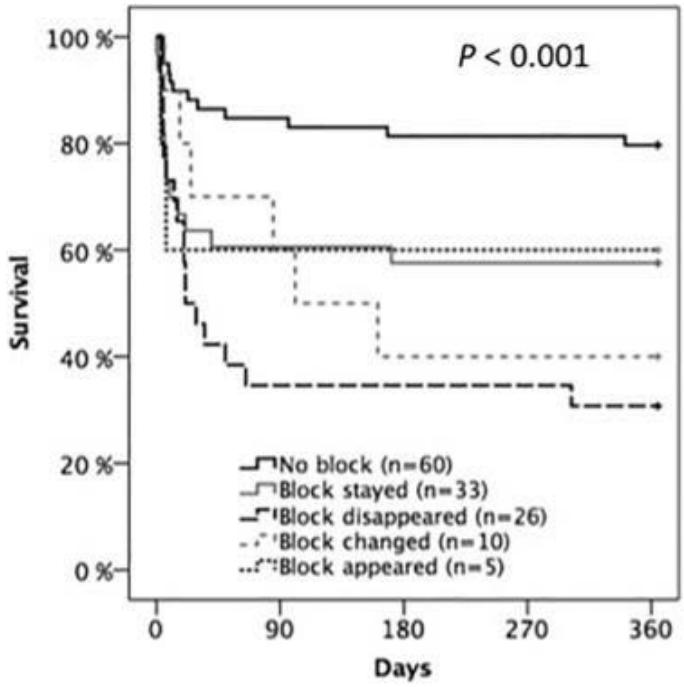


Figure 11 One-year Kaplan Meier curves in patients with different temporal evolution of ventricular conduction blocks. Block disappeared = transient block. Reproduced with publishers permission from Study II (256).

5.3 SYNTAX scores in STEMI-related cardiogenic shock (III)

5.3.1 SYNTAX scores and angiographic findings

Study III included 61 patients with STEMI-related CS. Mean age was 67 ± 12 years and 85% were men. At baseline, median baseline SYNTAX score 1 was 22 (15–32). After wiring or thrombectomy, median baseline SYNTAX score 2 was 19 (11–30), significantly lower than the baseline SYNTAX score 1 ($p < 0.01$). After revascularization, median residual SYNTAX score was 7 (0–13), lower than SYNTAX score 1 and 2 (both $p < 0.01$).

Patients were divided into tertiles by the baseline SYNTAX score 1 value: the first tertile: ≤ 18 points, the second tertile: 19–27 points, and the third tertile: > 27 points. No differences appeared among the tertiles in age, gender, or most in comorbidities. Only the history of PCI was less common in the first tertile than in the second and third tertiles (n = 0, vs. n = 3 (15%) and n = 6 (30%), both $p < 0.05$).

Table 14 describes the baseline characteristics and angiographic features of the Study III patients. Complete revascularization (residual SYNTAX score 0) was achieved more often in the first (57%) and second (25%) tertiles than in the third tertile, in which none of the patients reached complete revascularization (both $p < 0.01$). Overall, residual SYNTAX score was lower in the first and the second tertiles in comparison with the third tertile (both $p < 0.01$). More than half of patients (36, 59%) had shock before PCI, but with no difference in either SYNTAX score whether the patient had shock before or after the procedure (Table 15).

For analysis of interobserver variability, Cohen's Kappa statistics was 0.59 (95% CI 0.40 to 0.78; $p < 0.01$) for baseline SYNTAX score and 0.65 (95% CI 0.32 to 0.97; $p < 0.001$) for residual SYNTAX score.

Table 14 Baseline characteristics and angiographic findings of Study III patients

	First tertile ≤ 18 points n = 21	Second tertile 19-27 points n = 20	Third tertile > 27 points n = 20	p
Age, years	62 ± 12	68 ± 13	70 ± 12	0.92
Male gender (%)	20 (95)	14 (70)	18 (90)	0.06
Coronary artery disease (%)	2 (10)	4 (20)	7 (35)	0.13
Previous PCI (%)	0 (0)	3 (15)	6 (30)	<0.01
LVEF, %	37 ± 15	34 ± 14	29 ± 9	0.17
SBP, mmHg	77 ± 23	77 ± 11	76 ± 12	0.98
Serum lactate, mmol/l	2.2 (1.2-3.2)	2.3 (1.7-6.3)	2.8 (2.1-4.4)	0.31
eGFR, ml/min/1.73m^2	88 (65-104)	78 (42-98)	67 (41-87)	0.15
hs-TnT, ng/l	2427 (849-6810)	7236 (3677-11943)	2889 (1828-8965)	0.04
NT-proBNP, ng/l	198 (133-942)	1471 (253-3977)	3914 (481-16551)	<0.01
Acute occlusive thrombosis (%)	12 (57)	15 (75)	12 (60)	0.45
Chronic total occlusion (%)	1 (4.8)	1 (5.0)	15 (75)	<0.01
One-vessel disease (%)	14 (67)	8 (42)	0 (0)	<0.01
Three-vessel disease (%)	1 (4.8)	2 (11)	11 (55)	<0.01
Multivessel disease (%)	7 (33)	11 (55)	20 (100)	<0.01
LM disease (%)	3 (14)	3 (16)	3 (15)	0.99
CS before angiography (%)	12 (57)	13 (65)	11 (55)	0.79
Time from shock to angiography, min	68 (23-112)	40 (15-86)	75 (15-90)	0.57
Time from angiography to shock, min	180 (60-300)	20 (15-75)	98 (45-175)	0.47
Multivessel PCI (%)	4 (19)	6 (30)	7 (35)	0.5
Residual SYNTAX score, pts	0 (0-5)	6 (1.0-10)	20 (10-28)	<0.01
Complete revascularization (%)	12 (57)	5 (25)	0 (0)	<0.01
TIMI 3 post-PCI (%)	14 (67)	12 (60)	14 (74)	0.66
IABP (%)	10 (48)	14 (70)	13 (65)	0.31

Data presented as counts (percentages), means ± SD or medians (IQR).
Abbreviations: CS = cardiogenic shock, eGFR= estimated glomerular filtration rate, hs-TnT = high-sensitive troponin T, IABP = intra-aortic balloon pump, LM = left main, LVEF = left ventricular ejection fraction, NT-proBNP = N-terminal pro-natriuretic peptide, PCI = percutaneous coronary intervention, SBP = systolic blood pressure, TIMI = Thrombolysis in Myocardial Infarction

Table 15 Baseline and residual SYNTAX scores in patients who developed shock before or after PCI.

	CS before revascularization, 36	CS after revascularization, 25	p
Baseline SYNTAX score, pts	22 (15-22)	22 (15-31)	0.84
Residual SYNTAX score, pts	7 (0-18)	6 (0-11)	0.56

Data presented as medians (IQR). Abbreviations: CS = cardiogenic shock

5.3.2 Prognostic value of SYNTAX scores

In 90-day follow-up, 26 (43%) patients died. In the first tertile, 90-day mortality rate was lowest (4, 19%,), and mortality was higher in the second (10, 50%) and the third tertiles (12, 60%) (p = 0.02, Figure 12A). Use of different residual SYNTAX score cutoff points (0, 8, or 12 points) produced no significant differences in 90-day mortality (Figure 12B-D).

Of the four multivariable models created, the first multivariable model included significant baseline covariates: age, LVEF, arterial blood lactate, eGFR, NT-proBNP, and TIMI 3 post-PCI. The other three models included baseline or residual SYNTAX score and either CardShock risk score (85), IABP-SHOCK II risk score (84), or GRACE risk score (82).

In multivariable analysis, baseline SYNTAX score was associated with mortality in adjusted analysis with covariates and the IABP-SHOCK II and GRACE risk scores, but not when adjusted for the CardShock risk score (Table 16A). Residual SYNTAX score as a continuous or a categorical variable was not associated with 90-day mortality in adjusted analyses (Table 16B).

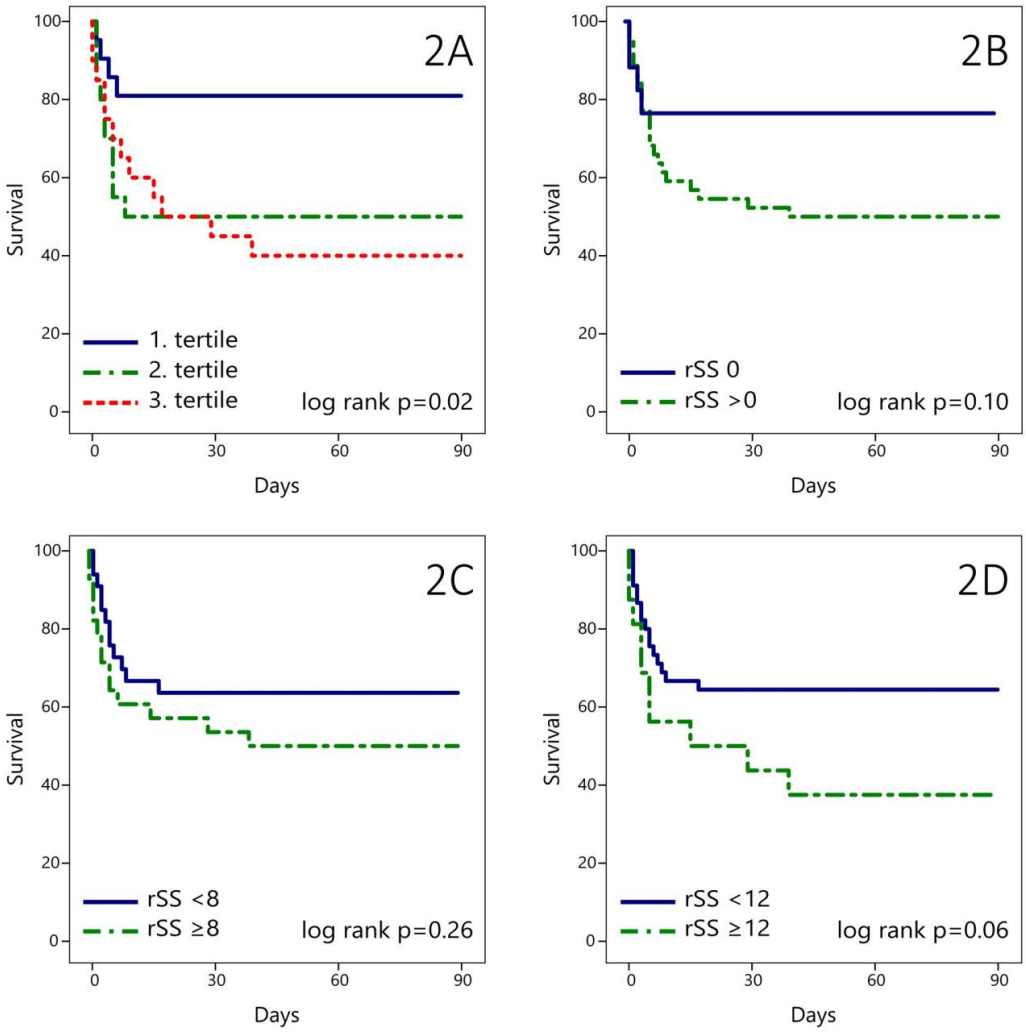


Figure 12 90-day Kaplan-Meier survival curves in baseline SYNTAX score tertiles (2a) and in different residual SYNTAX score (rSS) cutoff points (2b-d). Reproduced with publisher's permission from Study III (257).

Table 16 Multivariable mortality analysis with (A) baseline SYNTAX score and (B) residual SYNTAX score

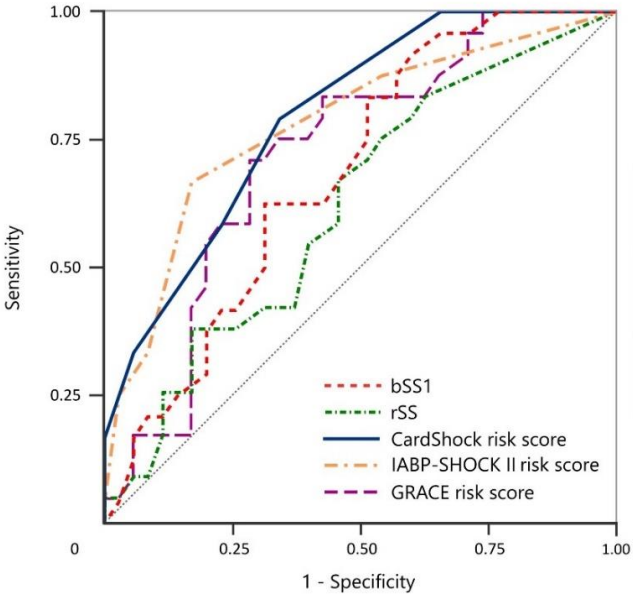
A)	HR	95% CI	p
bSS[a] + control variables[b]	1.06	1.01-1.10	0.03
bSS[a] + CardShock risk score	1.02	0.98-1.06	0.29
bSS[a] + IAPB-SHOCK II risk score	1.05	1.01-1.09	<0.01
bSS[a] + GRACE risk score	1.04	1.00-1.08	0.04
B)			
rSS[a] (continuous) + control variables[b]	1.03	0.99-1.08	0.14
rSS[a] (continuous) + CardShock risk score	1.02	0.98-1.06	0.44
rSS[a] (continuous) + IAPB-SHOCK II risk score	1.03	0.99-1.07	0.08
rSS[a] (continuous) + GRACE risk score	1.03	0.99-1.07	0.11
rSS>0 + control variables[b]	2.46	0.83-7.29	0.11
rSS>0 + CardShock risk score	2.41	0.80-7.26	0.12
rSS>0 + IAPB-SHOCK II risk score	2.05	0.70-6.00	0.19
rSS>0 + GRACE risk score	1.83	0.62-5.43	0.28
rSS≥8 + control variables[b]	1.27	0.55-2.94	0.58
rSS≥8 + CardShock risk score	1.05	0.48-2.31	0.91
rSS≥8 + IAPB-SHOCK II risk score	1.36	0.62-2.99	0.45
rSS≥8 + GRACE risk score	1.44	0.67-3.11	0.36
rSS≥12 + control variables[b]	1.54	0.65-3.66	0.33
rSS≥12 + CardShock risk score	1.26	0.55-2.88	0.58
rSS≥12 + IAPB-SHOCK II risk score	1.53	0.67-3.49	0.31
rSS≥12 + GRACE risk score	1.71	0.77-3.80	0.19

[a] per increase of 1 point.

[b] control variables: age, LVEF, arterial blood lactate, eGFR, NT-proBNP and TIMI 3 post-PCI

Abbreviations: bSS = baseline SYNTAX score, eGFR= estimated glomerular filtration rate, LVEF = left ventricular ejection fraction, NT-proBNP = N-terminal pro-natriuretic peptide, rSS = residual SYNTAX score, TIMI = Thrombolysis in Myocardial Infarction

For evaluation of risk assessment, the AUC of the baseline SYNTAX score 1 was 0.68 (95% CI 0.55 to 0.80), and the AUC of the residual SYNTAX score was 0.62 (0.48 to 0.74). The CardShock risk score had the highest AUC, 0.80 (95% CI 0.67 to 0.89) (Figure 13).



	AUC	95% CI	p-value
CardShock risk score	0.80	0.67-0.89	·
bSS1	0.68	0.55-0.80	0.13
rSS	0.62	0.48-0.74	0.03
IABP-SHOCK II risk score	0.78	0.65-0.88	·
bSS1	0.68	0.55-0.80	0.33
rSS	0.62	0.48-0.74	0.07
GRACE risk score	0.72	0.58-0.83	·
bSS1	0.68	0.55-0.80	0.13
rSS	0.62	0.48-0.74	0.03

Figure 13 ROCs and AUCs of the SYNTAX scores and the studied risk scores. Abbreviations: AUC = area under the curve, bSS = baseline SYNTAX score, ROC = receiver operating characteristic, rSS = residual SYNTAX score. Reproduced with publisher's permission from Study III (257).

5.4 Angiographic features in cardiogenic shock (IV)

5.4.1 Angiographic findings and procedural characteristics

Study IV included 158 CardShock patients with ACS-related CS. Median age was 67 ± 11 years, and 77% were men. One-vessel disease was the finding in 49 (31%) patients, two-vessel disease in 59 (37%), and three-vessel disease in 50 (32%). The most common IRA was LAD in 63 (40%) patients, followed by RCA in 48 (31%). LM as the IRA appeared in 19 (12%) (Figure 14).

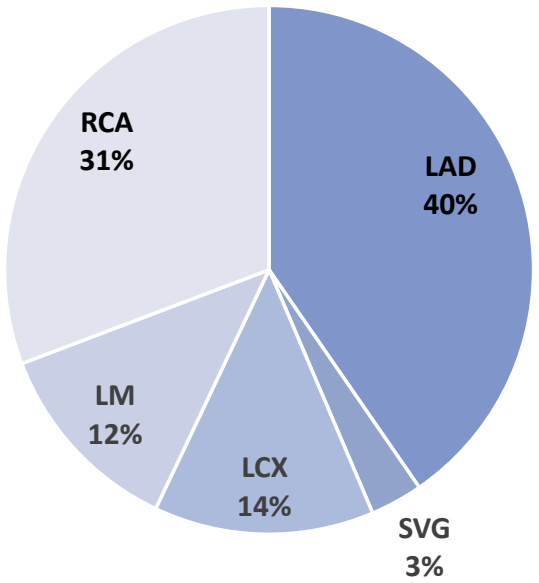


Figure 14 Prevalence of infarct-related arteries. Abbreviations: LAD = left anterior descending coronary artery, LCX = left circumflex coronary artery, LM = left main coronary artery, RCA = right coronary artery, SVG = saphenous vein graft

Almost all patients were treated with PCI (91%), and only eight patients were treated with CABG (9%) (Table 17). Successful revascularisation (TIMI 3 post-PCI) was achieved in 102 (72%). No difference in rate of successful revascularization emerged between the different IRAs (Figure 15). In addition, revascularization of the IRA was analysed between patients who developed shock before (n = 95) or after PCI (n = 49), and no difference was found in TIMI 3 flow post-PCI (68 % vs. 78 %; p = 0.31).

Table 17 Procedural characteristics of percutaneous coronary intervention

Procedural characteristics	All PCI treated patients, 144	Survivors, 82	Non-survivors, 62	p
Symptom-to-balloon time, min	340 (196-660)	335 (210-641)	340 (190-660)	0.70
Number of stents (%)				0.51
1	89 (65)	55 (69)	34 (60)	
2	32 (23)	18 (23)	14 (25)	
>3	10 (7)	5 (6)	5 (9)	
Bare metal stent (%)	66 (46)	39 (48)	27 (44)	0.76
Multivessel PCI (%)	38 (26)	21 (26)	17 (27)	0.96
PCI of LM (%)	21 (15)	8 (10)	13 (21)	0.11
Total occlusion (pre-PCI TIMI 0/1) (%)	119 (84)	65 (80)	54 (89)	0.27
TIMI post-PCI (%)				0.03
0/1	15 (11)	6 (7)	9 (15)	
2	25 (18)	10 (12)	15 (25)	
3	102 (72)	66 (81)	36 (60)	
Amount of contrast agent, ml	160 (120-220)	170 (120-210)	160 (124-250)	0.66
Shock after PCI (%)	49 (36)	33 (41)	16 (28)	0.16

Data presented as counts (percentages) or medians (IQR).

Abbreviations: LM = left main, PCI = percutaneous coronary intervention, TIMI = thrombolysis in myocardial infarction

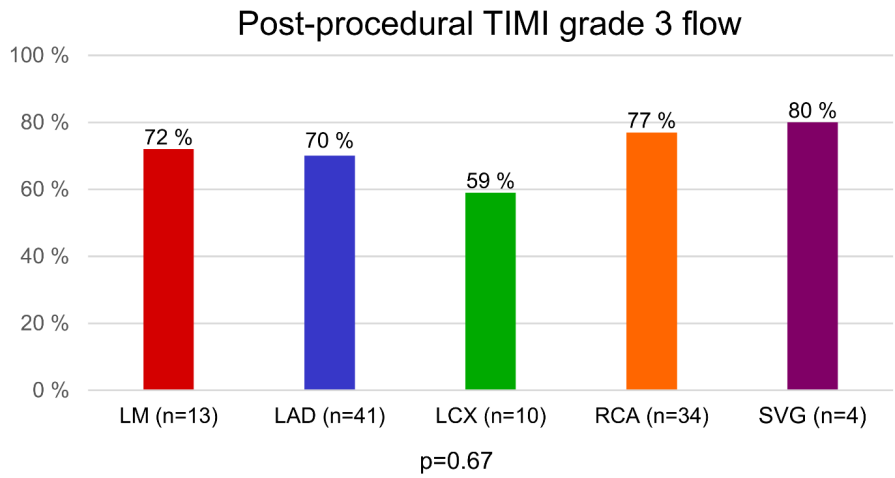


Figure 15 Percentages of patients who had TIMI 3 flow post-PCI. Abbreviations: LAD = left anterior descending coronary artery, LCX = left circumflex coronary artery, LM = left main coronary artery, PCI = percutaneous coronary intervention, RCA = right coronary artery, SVG = saphenous vein graft

5.4.2 Prognostic effect of angiographic features and procedural success

Patients with one-vessel coronary artery disease had the lowest 90-day mortality rate; the mortality rate was higher in patients with two- or three-vessel coronary artery disease (25% vs. 48% vs. 52%; p = 0.018; Figure 16A). Mortality was numerically higher if the IRA was the LM (53%) or the LAD (48%) when compared to mortality with the IRA being the RCA (29%) or the LCX (24%) (Figure 16B). Successful revascularization of the IRA, i.e. TIMI 3 post-PCI, was achieved more often in survivors than in non-survivors (81% vs. 60%; p = 0.019, Table 17, Figure 16C).

In multivariable Cox regression analysis, multivessel coronary artery disease (HR 2.59, CI 95% 1.29 to 5.18; p = 0.007), TIMI flow < 3 post-PCI (HR 2.41, CI95% 1.4 to 4.15; p = 0.001), increasing lactate (HR 1.17, CI95% 1.11 to 1.23; p<0.001), and decreasing LVEF (HR 1.03, CI95% 1.01 to 1.06; p = 0.002) were independently associated with 90-day mortality.

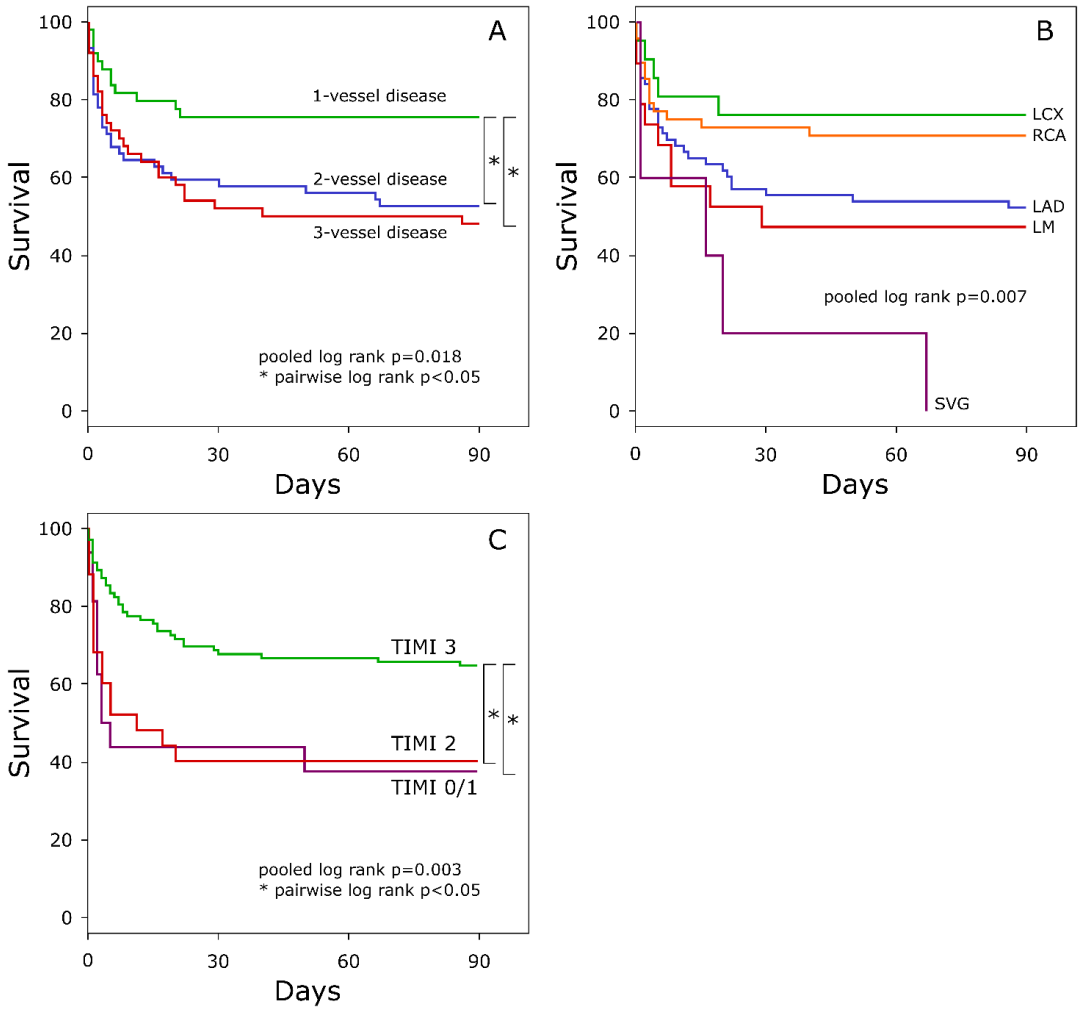


Figure 16 90-day Kaplan-Meier curves in patients with (A) different numbers of diseased coronary arteries, with (B) different IRAs and with (C) different TIMI-flow grades post-PCI. Abbreviations: LAD = left anterior descending coronary artery, LCX = left circumflex coronary artery, LM = left main coronary artery, RCA = right coronary artery, SVG = saphenous vein graft, TIMI = thrombolysis in myocardial infarction

5.4.3 Complications of percutaneous coronary intervention

Of the patients, one-third, 51 (35%) had a procedural complication, with no difference in rate of procedural complications between survivors and non-survivors (31% vs. 42%; p = 0.21). Most of the complications were arrhythmic: 19% had ventricular tachycardia or fibrillation, and 15% had bradycardia. Bradycardia was more frequent in non-survivors than in survivors (23% vs 9%; p = 0.034), but it was not associated with risk of 90-day death in adjusted analysis (HR 1.09, 95% CI 0.51 to 2.35; p = 0.82) (Table 18).

Table 18 Complications of percutaneous coronary intervention (PCI)

PCI Complications	All PCI treated patients, 144	Survivors, 82	Non-survivors, 62	p
Any PCI complication (%)	51 (35)	25 (31)	26 (42)	0.21
Ventricular tachycardia or fibrillation (%)	27 (19)	11 (13)	16 (26)	0.10
Bradycardia (%)	21 (15)	7 (9)	14 (23)	0.034
Dissection (%)	8 (6)	5 (6)	3 (5)	1.00
Tamponade (%)	1 (1)	1 (1)	0 (0)	1.00
Re-occlusion (%)	4 (3)	1 (1)	3 (5)	0.43
Re-coronary angiography (%)	12 (9)	10 (13)	2 (3)	0.10
Re-PCI (%)	10 (7)	8 (10)	2 (3)	0.22

Data presented as counts (percentages).

6 DISCUSSION

6.1 ST-segment deviations in cardiogenic shock

6.1.1 ST-segment deviations, CS aetiology, and patient characteristics

In Study I, the majority of CS patients with various CS aetiologies had ST-segment deviations in their baseline ECG. STE was the most common finding in half the patients, with STDEP being found in approximately one-third of these patients. In overall CS, the prevalence of ST-segment deviations has not been studied. In ACS, CS incidence has been two to three times higher in STEMI than in NSTEMI (11,60,62,210).

The high prevalence of ST-segment deviations reflects primarily the high prevalence of ACS aetiology in our Study I population. Especially in ACS patients, the higher prevalence of STE than of STDEP may be associated with different pathophysiologic mechanisms of ST-segment changes in the ischaemic setting. STE often results from total occlusion of the IRA (129), leading to transmural ischaemia (193) and to large areas of ischaemic myocardium, which is also supported by our finding of high troponin values in STE patients. STDEP, on the other hand, is more often the result of partial occlusion of the culprit artery and subendocardial ischaemia (205). In addition, as earlier evident in NSTEMI, two-thirds of the occluded culprit arteries already have collateral circulation (258,259), suggesting that in many cases the occlusion has an earlier origin. One may hypothesize that the collaterals often found in NSTEMI could protect against development of CS, which may explain the higher prevalence of STE in CS than in STDEP.

Of the studied ST-segment patterns, in particular STE was associated with ACS aetiology. CS was the first manifestation of heart disease in the majority of STE patients, nearly all of whom had ACS, and smoking was an important factor. The second most common CS aetiology was exacerbation of chronic heart failure, in which the cause of STE may be ischaemic cardiomyopathy caused by previous myocardial infarction with extensive scarring and chronically elevated ST-segment levels. Other causes of CS were valvular dysfunction and myocarditis, but interestingly, none of our patients with stress-induced cardiomyopathy had STE. The most common localisation of STE was anterior in half of our patients, suggesting the occlusion of the LAD (201).

Roughly one-third of our patients with STDEP had no ACS. Patients with STDEP were in their old age and had a high prevalence of previous diagnoses of coronary artery disease, chronic heart failure, and atrial fibrillation. Hence, the second most common aetiology in this group was exacerbation of chronic heart failure, followed by valvular dysfunction,

myocarditis, and stress-induced cardiomyopathy. In patients with aetiology other than ACS, the cause of STDEP may have been secondary ischaemia due to an imbalance between oxygen supply and demand, for example in patients with severely low blood pressure (48). Thus, in CS patients, STE implies most straightforwardly ACS, while in patients with STDEP, other aetiologies must be considered.

In patients without ST-segment deviation, ACS was still the main cause of CS in two-thirds of the patients. The other causes were exacerbation of chronic heart failure in roughly one-third, followed by stress-induced cardiomyopathy and by myocarditis. This reminds us that in CS, ACS is the most common cause, even though no ST-segment deviations are visible in the ECG.

6.1.2 Prognostic effect of ST-segment deviations

We studied mortality rates in the entire patient cohort with its various CS aetiologies, and separately studied the subgroup with ACS aetiology. In the entire study cohort, STE was associated with higher mortality than were other ST-segment patterns. This finding most likely is associated with the fact that STE occurred almost only in patients with ACS aetiology, and those with ACS tended to suffer from higher mortality rates than did patients with other CS aetiologies. No other study, to our knowledge, has reported mortality rates related to ST-segment patterns in patients with unselected CS aetiology.

In the ACS subgroup, no difference emerged in survival rates between patients with differing ST-segment patterns. Generally, in ACS, STEMI proves to be related to a higher in-hospital mortality rate than does NSTEMI, but their long-term prognoses are similar (260–264). Mortality rates for STEMI and NSTEMI in CS are controversial. Three CS studies reported NSTEMI patients to have higher mortality than do STEMI patients (60,62,210), but two other studies found no difference in survival (11,211). Comparing the differences between earlier CS studies and ours shows that in our study, the rates of coronary angiography (91%) and PCI (82%) in NSTEMI patients were higher than were earlier rates of coronary angiography ranging between 41% and 72% and PCI 13% and 72% (62,135,210,211). Furthermore, we found no difference in rates of coronary angiography and PCI between STEMI and NSTEMI patients, whereas other studies have reported significantly lower rates of invasive treatment in NSTEMI than in STEMI (60,62,210,211). It is thus possible that our extensive rate of revascularisation in NSTEMI patients was associated with better survival, which resulted in similar mortality rates as in STEMI. This finding highlights the importance of emergent coronary angiography and PCI for all ACS-related CS patients, regardless of ST-segment pattern.

6.2 Ventricular conduction blocks in cardiogenic shock

6.2.1 Prevalence of ventricular conduction blocks

In Study II, the prevalence of any ventricular conduction disturbance in baseline ECG was high, because half the patients had a ventricular conduction disturbance. The most prevalent findings were IVCD and isolated hemiblocks, both in 16% of the patients, followed by RBBB + hemiblock in 9%, isolated RBBB in 5%, and LBBB in 4%. Earlier CS findings showed a prevalence of RBBB from 13% to 20% and of LBBB from 2% to 10%, values thus similar to ours (11,20,209). The high prevalence of hemiblocks, isolated or associated with RBBB, was an interesting finding, as they have not been studied in the context of ACS-related CS before. Overall, in ACS patients, the prevalence of RBBB has been somewhat lower, but the prevalence of LBBB has been similar (13–16). Like our results, the incidence of LAHB in ACS has been estimated at 7% to 15% (265–268).

6.2.2 Association of ventricular conduction with patient characteristics

We found that patients with any ventricular conduction disturbance, when compared to patients with normal ventricular conduction, were older, had lower LVEF, higher troponin levels, and had the LM coronary artery more often as the IRA. Patients with RBBB + hemiblock had an especially high risk profile, as they had a low LVEF of 30%, high troponin levels, and the LM as the IRA in 18%. In contrast, in patients with isolated RBBB, LVEF was only moderately lowered at 47%, levels of troponin were lower, and none had the LM as the IRA. Patients with LBBB were older and had a high prevalence of chronic heart failure and coronary artery disease and a low ejection fraction. Similar to our results, in ACS-related CS, both LBBB and RBBB have been associated with lower ejection fraction, higher prevalence of comorbidities, and a higher rate of the LM as the IRA (11). Furthermore, in one contemporary study, those patients with RBBB + hemiblock rather than isolated RBBB were older, had a higher prevalence of comorbidities and a lower ejection fraction, and more often had three-vessel disease and the LAD as their IRA (13).

6.2.3 Temporal evolution of ventricular conduction blocks

In Study II, among those patients who showed a ventricular conduction block at baseline, one-fourth of the blocks reversed, and 10% changed into another block. None of the transient blocks were present in the patients' previous ECGs, suggesting that the blocks resulted from acute myocardial ischaemia

(17,18,222). Many of the transient blocks were hemiblocks associated with or without RBBB, which may result from slowed myocardial conduction leading to an axis deviation comparable to hemiblock, a phenomenon that may corrected by appropriate revascularization (9,222,228). The temporal evolution of conduction blocks has not been evaluated in CS, but in ACS, the rate of new-onset block reversion has been reported as high as 49% to 77% (16,19), similar to our findings. The block reversion rate was lowest in patients with RBBB and LBBB, implying that many of these changes may be of earlier origin.

6.2.4 Prognostic value of ventricular conduction blocks

We discovered that patients with any ventricular conduction block had two-fold higher mortality in than did patients with normal ventricular conduction. This result may be in part explained by the fact that changes in QRS duration and morphology reflect critical myocardial ischaemia (9,229), which subsequently may predict a poor prognosis. Even though the patients with ventricular conduction blocks were older, with more comorbidities and more severe coronary artery disease, the association with mortality was independent of baseline and clinical characteristics, as well as of the findings of coronary angiography and the success of revascularization.

When we examined ventricular conduction blocks separately, especially RBBB + hemiblock and isolated hemiblocks were independently associated with mortality. In addition, LBBB and isolated RBBB tended to be associated with mortality. In one study of ACS-related CS, RBBB was associated with worse survival in than was STEMI, but that study did not cover hemiblocks (11). Our study is thus, to our knowledge, the first to show the association of hemiblocks and mortality in CS patients. In overall ACS, the negative prognostic impact of ventricular conduction blocks has been evident (11,12,14–16).

In addition, we evaluated the association of temporal block evolution and mortality. Mortality was highest in patients with transient block, a result conflicting with earlier ACS findings (12,16). We hypothesised that the explanation for this difference consists of multiple factors. Many of the transient blocks we recorded were of new origin, which has been associated with poor prognosis in ACS (13,14,16). Secondly, the reversal of ventricular conduction disturbances has been thought to associate with restoration of coronary circulation (20), which in general in ACS is a good sign. However, in CS, because the state of shock has already developed, factors other than successful revascularization will contribute to mortality, such as haemodynamic instability and multiorgan failure; therefore, reversion of the block may lack the same effect as in general in ACS. In addition, the excess mortality in patients with reversible block did not only consist of early

mortality, but also of later deaths, suggesting mechanisms of mortality other than acute haemodynamic instability. Indeed, patients with transient block had the highest troponin values, indicating major myocardial damage and thus possible scarring, which in turn may have predisposed to arrhythmic events and sudden cardiac death.

6.3 Angiographic features in cardiogenic shock

6.3.1 Features of coronary artery disease

We found that the majority of patients with ACS-related CS had complex coronary artery disease (III and IV). In Study IV, one-third of the patients had two-vessel disease and one-third three-vessel disease. In STEMI-related CS (III), the prevalence of two-vessel disease was higher at 40% and three-vessel disease lower at 23%. Our finding of a high prevalence of multivessel disease is in accordance with other CS study findings, even though our prevalence of three-vessel disease was slightly lower than described (25,27,28,121,122).

In Study IV, LAD was the most common culprit artery in 40%, followed by RCA in 31%, LCX in 14%, LM in 12%, and saphenous vein graft (SVG) in 3%, corresponding to previous findings (23,25,27). LAD as the predominant culprit artery in patients with CS is comprehensible, since LAD occlusion has been associated in STEMI with increased risk for de-novo heart failure (269), and anterior myocardial infarction has been associated with risk for CS in STEMI patients with multivessel disease (270).

In Study III, the median baseline SYNTAX score at baseline was 22 (IQR 15-32) points, higher than previously described in CS (17 ± 10 points) (180), but the definition of CS in our study was stricter. The baseline SYNTAX score was also higher than in other studies with STEMI patients (36,37,175,177). Accordingly, earlier studies have shown that CS incidence was higher in STEMI patients with a high SYNTAX score (36,177) and that higher SYNTAX score was a predictor of CS in patients with acute myocardial infarction (180).

6.3.2 Characteristics of percutaneous coronary intervention

In Study IV, 91% of the CS patients with ACS aetiology underwent PCI procedure, which is similar to data in contemporary CS studies (24,28). IABP was utilized in 65% of our patients, reflecting the fact that results of the IABP-SHOCK II trial were then unavailable, because the recruitment periods were overlapping (105). Multivessel PCI was performed in one-fourth of the patients, roughly corresponding to the rates in other studies (23,120,143).

Successful revascularization (TIMI 3 post-PCI) occurred in 72% of the patients, a similar rate as in the IABP-SHOCK trial (24), yet a distinctly lower rate than reported overall in STEMI or NSTEMI, with successful revascularization in over 90% (271,272). The reason for lower PCI success rates in CS than in overall ACS may be associated with the facts that patients with CS have more complex lesions and that haemodynamic instability may interfere with the challenging PCI procedure. However, no difference in the rate of successful revascularization emerged between the IRAs, a result similar to that of the IABP-SHOCK trial (24). A distinctive reduction from baseline to residual SYNTAX score appeared, which implies that revascularization improved coronary artery circulation as anticipated. However, the residual SYNTAX score was higher than earlier described in STEMI (37), and the rate of complete revascularization (residual SYNTAX score 0) was lower than in overall patients treated with PCI (181,183–185), which reflects the complexity of CS patients' coronary artery disease.

Nearly half the patients presented with shock only after PCI, in accordance with the fact that most patients develop shock only after hospital admission (1,10,60,61), and that urgent revascularization is a strong recommendation in STEMI (109). However, no difference arose in success of revascularization (measured as TIMI 3 post-PCI or residual SYNTAX score) between patients who developed CS before or after PCI. This suggests that the cause of CS was not failure of revascularization. Furthermore, most study patients who developed CS after revascularization did so during the first hours after angiography, suggesting that the pathophysiological CS changes had probably started even before coronary angiography. The delay from symptom onset to PCI treatment was surprisingly long, with a median time of 6 hours, but any data regarding patient-related delays or transfer times was unavailable. In addition, 11% received thrombolysis before revascularization, which may partly explain the longer treatment delay.

6.3.3 Prognosis related to angiographic features and procedural success

In Study IV, multivessel disease was associated with worse survival, as also shown elsewhere (22,23,25–28). In addition, baseline SYNTAX score was associated with mortality in adjusted analysis with clinical covariates, as well as when adjusted with GRACE or with IABP-SHOCK II risk scores. This is in line with previous findings in STEMI patients, in which baseline SYNTAX score was credited with a robust predictive value (34–36). In addition, in ACS, baseline SYNTAX score was useful in risk stratification beyond the GRACE risk score. (273). However, the additive value of baseline SYNTAX Score in our study was marginal, which compromises the benefit of SYNTAX Score calculation for risk evaluation in CS. In our opinion, the clinical risk scores are more feasible and clinically accurate in CS risk stratification; assessing the

exact burden of coronary artery disease with baseline SYNTAX score may thus not be a wise use of resources.

We found that mortality was highest (100%) in patients with SVG as the IRA, followed by LM (53%), LAD (48%), RCA (29%), and LCX (24%). The dismal prognosis with SVG as the IRA may not only be associated with graft occlusion, but also with the comorbidities in a patient already treated with CABG. Overall, no statistically significant differences in outcome emerged between the different IRAs, a similar finding to that in a substudy of the IABP-SHOCK II trial (24). In other CS studies, LM has been associated with poor outcomes (23,25,27,31), whereas RCA as the IRA has been associated with better survival (26,32). Instinctively, it seems credible that LM as the culprit artery could be linked to poor outcome. However, it may be hypothesized that the culprit vessel with the corresponding area at risk only plays minor role in CS survival, especially when revascularization is successful; mortality may be more strongly associated with systemic alterations and multiorgan damage.

Studies III and IV revealed that successful revascularization of the IRA (TIMI 3 post-PCI) was associated with better survival, as shown previously (23–25,27–31,121,122). However, regarding completeness of revascularization, no association with residual SYNTAX score and survival appeared, even though residual SYNTAX scores have predicted mortality in overall ACS patients (37–39). The difference between our study population and earlier ACS studies is that our patients were critically ill; thus, their prognosis is related more often to factors other than the completeness of revascularization. In critically ill CS patients, treatment goals must include not only successful revascularization but also management of haemodynamic stability, prevention of multiorgan dysfunction, and management of ventilation support. In this context, complicated PCI procedures targeting low residual SYNTAX score may even worsen a patient's condition. Again, however, successful revascularization of the IRA was independently associated with better survival, which highlights the importance of restoring IRA blood flow, whereas aiming at complete revascularization may prove excessive. The message is similar to that of the CULPRIT-SHOCK trial, in which PCI treatment of the culprit lesion alone was associated with better outcomes than with multivessel PCI (151).

In Study IV, the symptom-to-balloon time was rather prolonged, with a median delay of 6 hours. No difference appeared in symptom-to-balloon time between survivors and non-survivors, a similar finding as that of the SHOCK trial, in which shock-onset-to-balloon time was also prolonged at 5 hours, with no association with shock-onset-to-balloon time and mortality (121). Others have, however, found that, in CS, shorter symptom-onset-to-balloon time (25,138), shorter first medical contact-to-balloon (136,137) and shorter door-to-balloon (138) time were associated with better survival. One crucial difference between our study and these was that we also included

patients who developed CS only after PCI. That may explain the longer delay from symptom-to-balloon and may also be the reason that longer delay did not lead to significantly higher mortality. In addition, some of the patients were treated with thrombolysis, which could cause a longer delay from symptom to balloon, and in which case longer delay may not contribute to mortality.

6.3.4 Procedural complications of percutaneous coronary intervention

In Study IV, procedural complications occurred in one-third of the patients, the most common being arrhythmic complications. Ventricular tachycardia or fibrillation was discovered in 19% and bradycardia in 15%. Overall, the rate of procedural complications during PCI was higher than previously in STEMI (33), and also higher than in a registry study of ACS-related CS (31). One may hypothesize that most of the arrhythmic events relate to the severity of the acute cardiac illness, and not just to the revascularization procedure itself. Indeed, complications were not associated with mortality, suggesting that they were treatable and transient. In addition to arrhythmias provoked by the cardiac instability and the PCI procedure, reperfusion arrhythmias are also possible in ACS-related CS (274). As our results show a high prevalence of arrhythmic events during PCI, immediate action such as defibrillation and cardiac pacing should be readily available for management of arrhythmic complications.

6.4 Limitations

Some limitations in this thesis are apparent. Regarding Studies I and II, it is essential to acknowledge the dynamic nature of ECG. Especially in the context of ACS, the ECG, and especially the ST-segment pattern, could change within minutes if there occurred an alteration in myocardial ischaemia such as rapid reperfusion or new occlusion of the coronary artery. However, we believe that these studies with one analysed baseline ECG per patient reflects clinical practice, for ECG is only one part of decision-making in a critical situation, and ECG may not be repeated especially in the first busy moments of CS management. In Study II, another limitation was the lack of earlier ECGs in many study patients, even after our retrospective search. This reflects, however, real-life practice, as CS patients are most often referred to a tertiary care center, where their previous ECGs may be unavailable. In addition, due to high early mortality, the number of patients with serial ECGs in Study II was low. Still, Study II, to our knowledge, involved the largest cohort in an examination of serial ECGs in the context of CS.

In general, one important limitation of this study is its sample size. Even though this study's sample was considerable for a prospective study of CS, the number of patients in some groups was low: around 20 patients in Study III. However, Study III was the first, and the largest study to analyse baseline and residual SYNTAX scores. Another limitation in Study III was that the interpretation of the angiograms was not centralized; rather, the SYNTAX scores were analysed in each hospital by one local experienced cardiologist. However, both were well trained to calculate the SYNTAX score, with no difference in interobserver agreement. Similarly, in Study IV, examination of the angiograms was not centralized, but the results were reported by the treating interventional cardiologists.

6.5 Clinical implications and future directions

This prospective CardShock study represents real-life CS patients with various CS aetiologies. Research in critically ill patients is challenging, which underlines the importance of multinational studies like the CardShock study.

We showed that, in CS, despite the development of more refined imagining techniques, ECG is still a useful tool in diagnostics and in assessment of prognosis. As stated in the guidelines (109), ECG should be one of the first measurements in critically ill patients, as it provides us with valuable information on the causes of CS and its prognosis. We showed that evaluation of the ST-segment pattern is useful in diagnostics, as most of the STE patients have ACS as the cause of their CS. On the other hand, along with the findings of STDEP and NSTD, other causes for CS aetiology need consideration, with corresponding diagnostic efforts, such as prompt echocardiography. Nevertheless, urgent angiography should be essential in every CS patient regardless of ST-segment changes, because ACS is still the most common cause of CS in each patient group despite differing ST-segment patterns.

In addition to ST-segment pattern, QRS configuration demands careful analysis, because ventricular conduction blocks, even hemiblocks, are associated with worse prognosis. The dismal prognosis of RBBB was recently acknowledged; the most recent European STEMI guideline included RBBB, along with LBBB, as the indication for urgent revascularization (109). The clinical value of IVCD and hemiblocks is still debatable, but our findings show that, their negative prognostic value should be recognised, with corresponding treatment efforts. Especially those CS patients with transient block face high mortality rates, which necessitates repeated ECG recordings during hospital stay and more intensive follow-up in those patients with an evolving QRS pattern. Interestingly, the mortality rates in patients with transient block were higher even after the early phase, which may have been associated with large infarctions leading to scarring and arrhythmic events. Thus, the finding of a

transient block may argue for more comprehensive analysis of myocardial damage, for example cardiac magnetic resonance imaging, and for more precise heart rhythm monitoring.

In CS patients with ACS, the mainstay of treatment is urgent coronary angiography and revascularization. The patients with multivessel disease are at high mortality risk, which necessitates close-up monitoring and more active management. Crucial for improvement of outcome is successful revascularization of the IRA, even if the procedure is delayed. However, targeting immediate complete revascularization does not improve survival, a similar finding with the CULPRIT-SHOCK trial (151), also acknowledged in the updated guidelines of myocardial revascularization (87). Regrettably, the result of PCI in CS patients was not optimal, with the successful revascularization rate of the IRA being lower than recorded previously in ACS patients overall, an important finding to be addressed. Complications during the PCI procedure are common, with arrhythmias especially abundant. Any complications should be prevented, if possible, but the occurrence of a complication is not fatal, because the complications were treatable and not associated with increased mortality.

7 CONCLUSIONS

The present thesis was designed to assess electrocardiographic and angiographic features in CS patients. ECG is an important tool for differentiating CS aetiology. In addition, ECG is useful in risk assessment, because STE and ventricular conduction blocks were markers of high mortality. In addition to ECG, some angiographic features may be useful in assessment of prognosis. Multivessel disease carried a high mortality risk, and successful revascularization of the IRA was associated with better outcome.

Baseline ECG in patients with CS was distinctively aberrant, with a high prevalence of ST-segment deviations (I) and ventricular conduction disturbances (II). In CS patients with various aetiologies, STE was associated with ACS aetiology, but, surprisingly, one-third of the patients with STDEP had no ACS. However, STDEP was associated with a high burden of previously diagnosed coronary artery disease and other comorbidities (I). Like STDEP, ventricular conduction disturbances occurred more often found in older patients with a higher burden of comorbidities (II).

In patients with various aetiologies, STE was associated with high mortality. In the subgroup of ACS-related CS, no difference in revascularization or mortality rates emerged among the ST-segment patterns (I). In ACS-related CS, any ventricular conduction disturbance on baseline ECG was associated with worse prognosis, but the later reversal of the block was not associated with better survival (II).

In patients with ACS-related CS, complex coronary artery disease was extremely common (III and IV). In STEMI-related CS, high values of the baseline and residual SYNTAX score were frequent, but their additive value in risk prediction beyond clinical assessment and risk scores was marginal (III). Multivessel disease was associated with poor prognosis. The crucial prognostic factor proved to be successful revascularization of the IRA (TIMI 3 post-PCI) (III and IV), and even delayed PCI seemed to be associated with better prognosis (IV). In ACS-related CS patients undergoing PCI, arrhythmic complications were common, but they were not associated with excess mortality (IV).

REFERENCES

1. De Luca L, Olivari Z, Farina A, Gonzini L, Lucci D, Di Chiara A, Casella G, Chiarella F, Boccanelli A, Di Pasquale G et al. Temporal trends in the epidemiology, management, and outcome of patients with cardiogenic shock complicating acute coronary syndromes. Eur J Heart Fail. 2015;17(11):1124–32.

2. Shah M, Patnaik S, Patel B, Ram P, Garg L, Agarwal M, Agrawal S, Arora S, Patel N, Wald J et al. Trends in mechanical circulatory support use and hospital mortality among patients with acute myocardial infarction and non-infarction related cardiogenic shock in the United States. Clin Res Cardiol. 2017;107(4):287–303.

3. van Diepen S, Katz JN, Albert NM, Henry TD, Jacobs AK, Kapur NK, Kilic A, Menon V, Ohman EM, Sweitzer NK et al. Contemporary Management of Cardiogenic Shock: A Scientific Statement From the American Heart Association. Circulation. 2017;136(16):e232–e268.

4. Goldberg RJ, Spencer FA, Gore JM, Lessard D, Yarzebski J. Thirty-Year Trends (1975 to 2005) in the Magnitude of, Management of, and Hospital Death Rates Associated With Cardiogenic Shock in Patients With Acute Myocardial Infarction. Circulation. 2009;119(9):1211–9.

5. Hunziker L, Radovanovic D, Jeger R, Pedrazzini G, Cuculi F, Urban P, Erne P, Rickli H, Pilgrim T, Hess F et al. Twenty-Year Trends in the Incidence and Outcome of Cardiogenic Shock in AMIS Plus Registry. Circ Cardiovasc Interv. 2019;12(4):e007293.

6. Schocken DD. Electrocardiographic left ventricular strain pattern: everything old is new again. J Electrocardiol. 2014;47(5):595–8.

7. Edhouse J, Brady WJ, Morris F. ABC of clinical electrocardiography: Acute myocardial infarction-Part II. BMJ. 2002;324(7343):963–6.

8. Wang K, Asinger RW, Marriott HJL. ST-Segment Elevation in Conditions Other Than Acute Myocardial Infarction. N Engl J Med. 2003;349(22):2128–35.

9. Birnbaum Y, Sclarovsky S. The grades of ischemia on the presenting electrocardiogram of patients with ST elevation acute myocardial infarction. J Electrocardiol. 2001;34(4):17–26.

10. Nguyen HL, Yarzebski J, Lessard D, Gore JM, McManus DD, Goldberg RJ. Ten-Year (2001-2011) Trends in the Incidence Rates and Short-Term Outcomes of Early Versus Late Onset Cardiogenic Shock After Hospitalization for Acute Myocardial Infarction. J Am Heart Assoc. 2017;6(6):e005566.

11. Jakl M, Stasek J, Kala P, Rokyta R, Kanovsky J, Ondrus T, Hromadka M, Widimsky P. Acute myocardial infarction complicated by shock: outcome analysis based on initial electrocardiogram. Scand Cardiovasc J. 2014;48(1):13–9.

12. Sgarbossa EB, Pinski SL, Topol EJ, Califf RM, Barbagelata A, Goodman SG, Gates KB, Granger CB, Miller DP, Underwood DA et al. Acute Myocardial Infarction and Complete Bundle Branch Block at Hospital Admission: Clinical Characteristics and Outcome in the Thrombolytic Era. J Am Coll Cardiol. 1998;31(1):105–10.

13. Widimsky P, Rohac F, Stasek J, Kala P, Rokyta R, Kuzmanov B, Jakl M, Poloczek M, Kanovsky J, Bernat I et al. Primary angioplasty in acute myocardial infarction with right bundle branch block: should new onset right bundle branch block be added to future guidelines as an indication for reperfusion therapy? Eur Heart J. 2012;33(1):86–95.

14. Melgarejo-Moreno A, Galcerá-Tomás J, Garcia-Alberolam A. Prognostic significance of bundle-branch block in acute myocardial infarction: The importance of location and time of appearance. Clin Cardiol. 2001;24(5):371–6.

15. Guerrero M, Harjai K, Stone GW, Brodie B, Cox D, Boura J, Grines L, O'Neill W, Grines C. Comparison of the prognostic effect of left versus right versus no bundle branch block on presenting electrocardiogram in acute myocardial infarction patients treated with primary angioplasty in the primary angioplasty in myocardial infarction trials. Am J Cardiol. 2005;96(4):482–8.

16. Melgarejo-Moreno A, Galcerá-Tomás J, García-Alberola A, Valdés-Chavarri M, Castillo-Soria FJ, Mira-Sánchez E, Gil-Sánchez J, Allegue-Gallego J. Incidence, Clinical Characteristics, and Prognostic Significance of Right Bundle-Branch Block in Acute Myocardial Infarction. Circulation. 1997;96(4):1139–44.

17. Surawicz B. Reversible QRS changes during acute myocardial ischemia. J Electrocardiol. 1998;31(3):209–20.

18. Wagner NB, Sevilla DC, Krucoff MW, Lee KL, Pieper KS, Kent KK, Bottner RK, Selvester RH, Wagner GS. Transient alterations of the QRS complex and ST segment during percutaneous transluminal balloon angioplasty of the left anterior descending coronary artery. Am J Cardiol. 1988;62(16):1038–42.

19. Newby KH, Pisano´ E, Krucoff MW, Green C, Natale A. Incidence and Clinical Relevance of the Occurrence of Bundle-Branch Block in Patients Treated With Thrombolytic Therapy. Circulation. 1996;94(10):2424–8.

20. White HD, Palmeri ST, Sleeper LA, French JK, Wong C-K, Lowe AM, Crapo JW, Koller PT, Baran KW, Boland JL et al. Electrocardiographic findings in cardiogenic shock, risk prediction, and the effects of emergency revascularization: Results from the SHOCK trial. Am Heart J. 2004;148(5):810–7.

21. Sakakura K, Kubo N, Hashimoto S, Ikeda N, Funayama H, Hirahara T, Sugawara Y, Yasu T, Ako J, Kawakami M et al. Determinants of in-hospital death in left main coronary artery myocardial infarction complicated by cardiogenic shock. J Cardiol. 2008;52(1):24–9.

22. Hoebers LP, Vis MM, Claessen BE, van der Schaaf RJ, Kikkert WJ, Baan J, de Winter RJ, Piek JJ, Tijssen JGP, Dangas GD et al. The impact of multivessel disease with and without a co-existing chronic total occlusion on short- and long-term mortality in ST-elevation myocardial infarction patients with and without cardiogenic shock. Eur J Heart Fail. 2013;15(4):425–32.

23. Trzeciak P, Gierlotka M, Gąsior M, Lekston A, Wilczek K, Słonka G, Kalarus Z, Zembala M, Hudzik B, Poloński L. Mortality of patients with ST-segment elevation myocardial infarction and cardiogenic shock treated by PCI is correlated to the infarct-related artery - Results from the PL-ACS Registry. Int J Cardiol. 2013;166(1):193–7.

24. Fuernau G, Fengler K, Desch S, Eitel I, Neumann F-J, Olbrich H-G, de Waha A, de Waha S, Richardt G, Hennersdorf M et al. Culprit lesion location and outcome in patients with cardiogenic shock complicating myocardial infarction: a substudy of the IABP-SHOCK II-trial. Clin Res Cardiol. 2016;105(12):1030–41.

25. Zeymer U, Vogt A, Zahn R, Weber MA, Tebbe U, Gottwik M, Bonzel T, Senges J, Neuhaus K-L. Predictors of in-hospital mortality in 1333 patients with acute myocardial infarction complicated by cardiogenic shock treated with primary percutaneous coronary intervention (PCI). Eur Heart J. 2004;25(4):322–8.

26. Sanborn TA, Sleeper LA, Webb JG, French JK, Bergman G, Parikh M, Wong SC, Boland J, Pfisterer M, Slater JN et al. Correlates of One-Year Survival in Patients with Cardiogenic Shock Complicating Acute Myocardial Infarction: Angiographic Findings from the SHOCK Trial. J Am Coll Cardiol. 2003;42(8):1373–9.

27. Wong SC, Sanborn T, Sleeper LA, Webb JG, Pilchik R, Hart D, Mejnartowicz S, Antonelli TA, Lange R, French JK et al. Angiographic findings and clinical correlates in patients with cardiogenic shock complicating acute myocardial infarction: A report from the SHOCK Trial Registry. J Am Coll Cardiol. 2000/09/14. 2000;36(3 SUPPL. A):1077–83.

28. Backhaus T, Fach A, Schmucker J, Fiehn E, Garstka D, Stehmeier J, Hambrecht R, Wienbergen H. Management and predictors of outcome in unselected patients with cardiogenic shock complicating acute ST-segment elevation myocardial infarction: results from the Bremen STEMI Registry. Clin Res Cardiol. 2018;107(5):371–9.

29. Tsai TH, Chai HT, Sun CK, Leu S, Fan CQ, Zhang ZH, Fang HY, Youssef AA, Hussein H, Yang CH et al. Comparison of 30-day mortality between anterior-wall versus inferior-wall st-segment elevation myocardial infarction complicated by cardiogenic shock in patients undergoing primary coronary angioplasty. Cardiology. 2010;116(2):144–50.

30. Hayiroğlu MI, Keskin M, Uzun AO, Yildirim DI, Kaya A, Çinier G, Bozbeyoğlu E, Yildirimtürk Ö, Kozan Ö, Pehlivanoğlu S. Predictors of In-Hospital Mortality in Patients With ST-Segment Elevation Myocardial Infarction Complicated With Cardiogenic Shock. Heart Lung and Circulation. 2019;237–44.

31. Kunadian V, Qiu W, Ludman P, Redwood S, Curzen N, Stables R, Gunn J, Gershlick A. Outcomes in patients with cardiogenic shock following percutaneous coronary intervention in the contemporary era: An analysis from the BCIS database (British Cardiovascular Intervention Society). JACC Cardiovasc Interv. 2014;7(12):1374–85.

32. Taniguchi Y, Sakakura K, Adachi Y, Akashi N, Watanabe Y, Noguchi M, Yamamoto K, Ugata Y, Wada H, Momomura S et al. In-hospital outcomes of acute myocardial infarction with cardiogenic shock caused by right coronary artery occlusion vs. left coronary artery occlusion. Cardiovasc Interv Ther. 2018;33(4):338–44.

33. Brener SJ, Witzenbichler B, Maehara A, Dizon J, Fahy M, El-Omar M, Dambrink JH, Genereux P, Mehran R, Oldroyd K et al. Infarct size and mortality in patients with proximal versus mid left anterior descending artery occlusion: The intracoronary abciximab and aspiration thrombectomy in patients with large anterior myocardial infarction (INFUSE-AMI) trial. Am Heart J. 2013;166(1):64–70.

34. Garg S, Sarno G, Serruys PW, Rodriguez AE, Bolognese L, Anselmi M, De Cesare N, Colangelo S, Moreno R, Gambetti S et al. Prediction of 1-Year Clinical Outcomes Using the SYNTAX Score in Patients With Acute ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention. JACC Cardiovasc Interv. 2011;4(1):66–75.

35. Onuk T, Gungor B, Ipek G, Karatas MB, Canga Y, Akyuz S, Haci R, Karadeniz FO, Sungur A, Kasikcioglu H et al. Comparison of long-term prognostic value of baseline SYNTAX and clinical SYNTAX scores in ST-segment elevation myocardial infarction patients with multivessel disease. Coron Artery Dis. 2016;27(4):311–8.

36. Magro M, Nauta S, Simsek C, Onuma Y, Garg S, van der Heide E, van der Giessen WJ, Boersma E, van Domburg RT, van Geuns RJ et al. Value of the SYNTAX score in patients treated by primary percutaneous coronary intervention for acute ST-elevation myocardial infarction: The MI SYNTAXscore study. Am Hear J. 2011;161(4):771–81.

37. Singbal Y, Fryer M, Garrahy P, Lim R. Baseline and residual SYNTAX score in predicting outcomes after acute infarct angioplasty. EuroIntervention. 2017;12(16):1995–2000.

38. Khan R, Al-Hawwas M, Hatem R, Azzalini L, Fortier A, Joliecoeur EM, Tanguay J-F, Lavoie-L'Allier P, Ly HQ. Prognostic impact of the residual SYNTAX score on in-hospital outcomes in patients undergoing primary percutaneous coronary intervention. Catheter Cardiovasc Interv. 2016;88(5):740–7.

39. Braga CG, Cid-Alvarez AB, Dieguez AR, Alvarez BA, Otero DL, Sanchez RO, Pena XS, Salvado VG, Trillo-Nouche R, Gonzalez-Juanatey JR. Prognostic impact of residual SYNTAX score in patients with ST-elevation myocardial infarction and multivessel disease: Analysis of an 8-year all-comers registry. Int J Cardiol. 2017;243(15):21–6.

40. Reynolds HR, Hochman JS. Cardiogenic shock: current concepts and improving outcomes. Circulation. 2008;117(5):686–97.

41. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Eur Heart J. 2016;37(27):2129–200.

42. Forrester JS, Diamond GA, Swan HJ. Correlative classification of clinical and hemodynamic function after acute myocardial infarction. Am J Cardiol. 1977;39(2):137–45.

43. Nohria A, Tsang SW, Fang JC, Lewis EF, Jarcho JA, Mudge GH, Stevenson LW. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. J Am Coll Cardiol. 2003;41(10):1797–804.

44. Mebazaa A, Combes A, van Diepen S, Hollinger A, Katz JN, Landoni G, Hajjar LA, Lassus J, Lebreton G, Montalescot G et al. Management of cardiogenic shock complicating myocardial infarction. Intensive Care Med. 2018;44(6):760–73.

45. Reyentovich A, Barghash MH, Hochman JS. Management of refractory cardiogenic shock. Nat Rev Cardiol. 2016;13(8):481–92.

46. Nieminen MS, Böhm M, Cowie MR, Drexler H, Filippatos GS, Jondeau G, Hasin Y, Lopez-Sendon J, Mebazaa A, Metra M et al. Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: The Task Force on Acute Heart Failure of the European Society of Cardiology. Eur Heart J. 2005;26(4):384–416.

47. Hochman JS, Buller CE, Sleeper LA, Boland J, Dzavik V, Sanborn TA, Godfrey E, White HD, Lim J, LeJemtel T. Cardiogenic shock complicating acute myocardial infarction—etiologies, management and outcome: a report from the SHOCK Trial Registry. J Am Coll Cardiol. 2000;36(3, Supplement 1):1063–70.

48. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD, Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth Universal Definition of Myocardial Infarction (2018). 2018;72(18):2231–64.

49. Heyndrickx GR. Early Reperfusion Phenomena. Semin Cardiothorac Vasc Anesth. 2006;10(3):236–41.

50. Pomblum VJ, Korbmacher B, Cleveland S, Sunderdiek U, Klocke RC, Schipke JD. Cardiac stunning in the clinic: the full picture. Interact Cardiovasc Thorac Surg. 2010;10(1):86–91.

51. Hollenberg SM, Kavinsky CJ, Parrillo JE. Cardiogenic Shock. Ann Intern Med. 1999;131(1):47–59.

52. Topalian S, Ginsberg F, Parrillo JE. Cardiogenic shock. Crit Care Med. 2008;36(1):S66-74.

53. Neumann F-J, Ott I, Gawaz M, Richardt G, Holzapfel H, Jochum M, Schömig A. Cardiac Release of Cytokines and Inflammatory Responses in Acute Myocardial Infarction. Circulation. 1995;92(4):748–55.

54. Li H, Förstermann U. Nitric oxide in the pathogenesis of vascular disease. J Pathol. 2000;190(3):244–54.

55. Kohsaka S, Menon V, Lowe AM, Lange M, Dzavik V, Sleeper LA, Hochman JS. Systemic Inflammatory Response Syndrome After Acute Myocardial Infarction Complicated by Cardiogenic Shock. Arch Intern Med. 2005;165(14):1643–50.

56. Hochman JS. Cardiogenic Shock Complicating Acute Myocardial Infarction: Expanding the Paradigm. Circulation. 2003;107(24):2998–3002.

57. Prondzinsky R, Unverzagt S, Lemm H, Wegener N-A, Schlitt A, Heinroth KM, Dietz S, Buerke U, Kellner P, Loppnow H et al. Interleukin-6, -7, -8 and -10 predict outcome in acute myocardial infarction complicated by cardiogenic shock. Clin Res Cardiol. 2012;101(5):375–84.

58. Parenica J, Jarkovsky J, Malaska J, Mebazaa A, Gottwaldova J, Helanova K, Litzman J, Dastych M, Tomandl J, Spinar J et al. Infectious Complications and Immune/Inflammatory Response in Cardiogenic Shock Patients: A Prospective Observational Study. Shock. 2016;47(2):165–74.

59. Stout KK, Verrier ED. Acute Valvular Regurgitation. Circulation. 2009;119(25):3232–41.

60. Jeger R V, Radovanovic D, Hunziker PR, Pfisterer ME, Stauffer J-C, Erne P, Urban P. Ten-Year Trends in the Incidence and Treatment of Cardiogenic Shock. Ann Intern Med. 2008;149(9):618–26.

61. Babaev A, Frederick PD, Pasta DJ, Every N, Sichrovsky T, Hochman JS, NRMI Investigators for the. Trends in Management and Outcomes of Patients With Acute Myocardial Infarction Complicated by Cardiogenic Shock. JAMA. 2005;294(4):448–54.

62. Anderson ML, Peterson ED, Peng SA, Wang TY, Ohman EM, Bhatt DL, Saucedo JF, Roe MT. Differences in the Profile, Treatment, and Prognosis of Patients With Cardiogenic Shock by Myocardial Infarction Classification: A Report From NCDR. Circ Cardiovasc Qual Outcomes. 2013;6(6):708–15.

63. Awad HH, Anderson FA, Gore JM, Goodman SG, Goldberg RJ. Cardiogenic shock complicating acute coronary syndromes: Insights from the Global Registry of Acute Coronary Events. Am Heart J. 2012;163(6):963–71.

64. Redfors B, Angeras O, Ramunddal T, Dworeck C, Haraldsson I, Ioanes D, Petursson P, Libungan B, Odenstedt J, Stewart J et al. 17-year trends in incidence and prognosis of cardiogenic shock in patients with acute myocardial infarction in western Sweden. Int J Cardiol. 2015;185:256–62.

65. Kolte, Khera S, Aronow WS, Mujib M, Palaniswamy C, Sule S, Jain D, Gotsis W, Ahmed A, Frishman WH et al. Trends in incidence, management, and outcomes of cardiogenic shock complicating ST-elevation myocardial infarction in the United States. J Am Hear Assoc. 2014;3(1):e000590.

66. Fang J, Mensah GA, Alderman MH, Croft JB. Trends in acute myocardial infarction complicated by cardiogenic shock, 1979-2003, United States. Am Heart J. 2006;152(6):1035–41.

67. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola V-P, Hochadel M, Komajda M, Lassus J, Lopez-Sendon JL et al. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. Eur Heart J. 2006;27(22):2725–36.

68. Siirila-Waris K, Lassus J, Melin J, Peuhkurinen K, Nieminen MS, Harjola V-P, FINN-AKVA Study Group. Characteristics, outcomes, and predictors of 1-year mortality in patients hospitalized for acute heart failure. Eur Heart J. 2006;27(24):3011–7.

69. Tavazzi L, Maggioni AP, Lucci D, Cacciatore G, Ansalone G, Oliva F, Porcu M, Italian survey on Acute Heart Failure Investigators. Nationwide survey on acute heart failure in cardiology ward services in Italy. Eur Heart J. 2005;27(10):1207–15.

70. Oliva F, Mortara A, Cacciatore G, Chinaglia A, Di Lenarda A, Gorini M, Metra M, Senni M, Maggioni AP, Tavazzi L et al. Acute heart failure patient profiles, management and in-hospital outcome: results of the Italian Registry on Heart Failure Outcome. Eur J Heart Fail. 2012;14(11):1208–17.

71. Chioncel O, Mebazaa A, Harjola V-P, Coats AJ, Piepoli MF, Crespo-Leiro MG, Laroche C, Seferovic PM, Anker SD, Ferrari R et al. Clinical phenotypes and outcome of patients hospitalized for acute heart failure: the ESC Heart Failure Long-Term Registry. Eur J Heart Fail. 2017;19(10):1242–54.

72. Di Vece D, Citro R, Cammann VL, Kato K, Gili S, Szawan KA, Micek J, Jurisic S, Ding KJ, Bacchi B et al. Outcomes Associated With Cardiogenic Shock in Takotsubo Syndrome. Circulation. 2019;139(3):413–5.

73. Stiermaier T, Eitel C, Desch S, Fuernau G, Schuler G, Thiele H, Eitel I. Incidence, determinants and prognostic relevance of cardiogenic shock in patients with Takotsubo cardiomyopathy. Eur Hear J Acute Cardiovasc Care. 2016;5(6):489–96.

74. Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, Cammann VL, Sarcon A, Geyer V, Neumann CA et al. Clinical Features and Outcomes of Takotsubo (Stress) Cardiomyopathy. N Engl J Med. 2015;373(10):929–38.

75. Killip T, Kimball JT. Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. Am J Cardiol. 1967;20(4):457–64.

76. Kalmanovich E, Blatt A, Brener S, Shlezinger M, Shlomo N, Vered Z, Hod H, Goldenberg I, Elbaz-Greener G. Trends in the management and outcomes of patients admitted with acute coronary syndrome complicated by cardiogenic shock over the past decade: Real world data from the acute coronary syndrome Israeli survey (ACSIS). Oncotarget. 2017;8(26):42876–86.

77. Carnendran L, Abboud R, Sleeper L., Gurunathan R, Webb J., Menon V, Dzavik V, Cocke T, Hochman for the SHOCK Investigators J. Trends in cardiogenic shock: report from the SHOCK Study. Eur Heart J. 2001;22(6):472–8.

78. Zannad F, Mebazaa A, Juillière Y, Cohen-Solal A, Guize L, Alla F, Rougé P, Blin P, Barlet M-H, Paolozzi L et al. Clinical profile, contemporary management and one-year mortality in patients with severe acute heart failure syndromes: The EFICA study. Eur J Heart Fail. 2006;8(7):697–705.

79. Shah RU, de Lemos JA, Wang TY, Chen AY, Thomas L, Sutton NR, Fang JC, Scirica BM, Henry TD, Granger CB. Post-Hospital Outcomes of Patients With Acute Myocardial Infarction With Cardiogenic Shock: Findings From the NCDR. J Am Coll Cardiol. 2016;67(7):739–47.

80. Singh M, White J, Hasdai D, Hodgson PK, Berger PB, Topol EJ, Califf RM, Holmes Jr DR. Long-Term Outcome and its Predictors Among Patients With ST-Segment Elevation Myocardial Infarction Complicated by Shock: Insights From the GUSTO-I Trial. J Am Coll Cardiol. 2007;50(18):1752–8.

81. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, Werf F Van de, Avezum Á, Goodman SG, Flather MD et al. Predictors of Hospital Mortality in the Global Registry of Acute Coronary Events. JAMA Intern Med. 2003;163(19):2345.

82. Fox KAA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, Avezum Á, Goodman SG, Flather MD, Anderson FA et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). BMJ. 2006;333(7578):1091–4.

83. Sleeper LA, Reynolds HR, White HD, Webb JG, Džavík V, Hochman JS. A severity scoring system for risk assessment of patients with cardiogenic shock: A report from the SHOCK Trial and Registry. Am Heart J. 2010;160(3):443–50.

84. Pöss J, Köster J, Fuernau G, Eitel I, de Waha S, Ouarrak T, Lassus J, Harjola VP, Zeymer U, Thiele H et al. Risk Stratification for Patients in Cardiogenic Shock After Acute Myocardial Infarction. J Am Coll Cardiol. 2017;69(15):1913–20.

85. Harjola V-P, Lassus J, Sionis A, Køber L, Tarvasmäki T, Spinar J, Parissis J, Banaszewski M, Silva-Cardoso J, Carubelli V et al. Clinical picture and risk prediction of short-term mortality in cardiogenic shock. Eur J Heart Fail. 2015;17(5):501–9.

86. Vahdatpour C, Collins D, Goldberg S. Cardiogenic Shock. J Am Heart Assoc. 2019;8(8):e011991.

87. Neumann F-J, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet J-P, Falk V, Head SJ et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2018;40(2):87–165.

88. Binanay C, Califf RM, Hasselblad V, O'Connor CM, Shah MR, Sopko G, Stevenson LW, Francis GS, Leier C V, Miller LW et al. Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness: The ESCAPE Trial. JAMA. 2005;294(13):1625–33.

89. Harvey S, Harrison DA, Singer M, Ashcroft J, Jones CM, Elbourne D, Brampton W, Williams D, Young D, Rowan K et al. Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial. Lancet. 2005;366(9484):472–7.

90. Shah MR, Hasselblad V, Stevenson LW, Binanay C, O'Connor CM, Sopko G, Califf RM. Impact of the Pulmonary Artery Catheter in Critically Ill Patients. JAMA. 2005;294(13):1664.

91. Cecconi M, De Backer D, Antonelli M, Beale R, Bakker J, Hofer C, Jaeschke R, Mebazaa A, Pinsky MR, Teboul JL et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. Intensive Care Med. 2014;40(12):1795–815.

92. Arbel Y, Mass R, Ziv-Baran T, Khoury S, Margolis G, Sadeh B, Flint N, Ben-Shoshan J, Finn T, Keren G et al. Prognostic implications of fluid balance in ST elevation myocardial infarction complicated by cardiogenic shock. Eur Hear J Acute Cardiovasc Care. 2017;6(5):462–7.

93. Levy B, Bastien O, Bendjelid K, Cariou A, Chouihed T, Combes A, Mebazaa A, Megarbane B, Plaisance P, Ouattara A et al. Experts' recommendations for the management of adult patients with cardiogenic shock. Ann Intensive Care. 2015;5(1):17.

94. Backer D, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med. 2010;362.

95. Léopold V, Gayat E, Pirracchio R, Spinar J, Parenica J, Tarvasmäki T, Lassus J, Harjola V-P, Champion S, Zannad F et al. Epinephrine and short-term survival in cardiogenic shock: an individual data meta-analysis of 2583 patients. Intensive Care Med. 2018;44(6):847–56.

96. Tarvasmäki T, Lassus J, Varpula M, Sionis A, Sund R, Køber L, Spinar J, Parissis J, Banaszewski M, Silva Cardoso J et al. Current real-life use of vasopressors and inotropes in cardiogenic shock - adrenaline use is associated with excess organ injury and mortality. Crit Care. 2016;20(1):1–11.

97. Levy B, Clere-Jehl R, Legras A, Morichau-Beauchant T, Leone M, Frederique G, Quenot J-P, Kimmoun A, Cariou A, Lassus J et al. Epinephrine Versus Norepinephrine for Cardiogenic Shock After Acute Myocardial Infarction. J Am Coll Cardiol. 2018;72(2):173–82.

98. Hollenberg SM. Vasoactive drugs in circulatory shock. Am J Respir Crit Care Med. 2011;183(7):847–55.

99. Overgaard CB, Džavík V. Inotropes and Vasopressors: Review of Physiology and Clinical Use in Cardiovascular Disease. Circulation. 2008;118(10):1047–56.

100. Haikala; PKPL, Pollesello P, Levijoki J, Haikala H. Effects of Levosimendan and Milrinone on Oxygen Consumption in Isolated Guinea-Pig Heart. J Cardiovasc Pharmacol. 2004;43(4):555–61.

101. Schumann J, Henrich EC, Strobl H, Prondzinsky R, Weiche S, Thiele H, Werdan K, Frantz S, Unverzagt S. Inotropic agents and vasodilator strategies for the treatment of cardiogenic shock or low cardiac output syndrome. Cochrane Database Syst Rev. 2018;(1).

102. Lewis TC, Aberle C, Altshuler D, Piper GL, Papadopoulos J. Comparative Effectiveness and Safety Between Milrinone or Dobutamine as Initial Inotrope Therapy in Cardiogenic Shock. J Cardiovasc Pharmacol Ther. 2019;24(2):130–8.

103. Sandhu A, McCoy LA, Negi SI, Hameed I, Atri P, Al'Aref SJ, Curtis J, McNulty E, Anderson HV, Shroff A et al. Use of Mechanical Circulatory Support in Patients Undergoing Percutaneous Coronary Intervention. Circulation. 2015;132(13):1243–51.

104. Kar B, Gregoric ID, Basra SS, Idelchik GM, Loyalka P. The Percutaneous Ventricular Assist Device in Severe Refractory Cardiogenic Shock. J Am Coll Cardiol. 2011;57(6):688–96.

105. Thiele H, Zeymer U, Neumann F-J, Ferenc M, Olbrich H-G, Hausleiter J, de Waha A, Richardt G, Hennersdorf M, Empen K et al. Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK II): final 12 month results of a randomised, open-label trial. Lancet. 2013;382(9905):1638–45.

106. Thiele H, Zeymer U, Neumann F-J, Ferenc M, Olbrich H-G, Hausleiter J, Richardt G, Hennersdorf M, Empen K, Fuernau G et al. Intraaortic Balloon Support for Myocardial Infarction with Cardiogenic Shock. N Engl J Med. 2012;367(14):1287–96.

107. Thiele H, Zeymer U, Thelemann N, Neumann F-J, Hausleiter J, Abdel-Wahab M, Meyer-Saraei R, Fuernau G, Eitel I, Hambrecht R et al. Intraaortic Balloon Pump in Cardiogenic Shock Complicating Acute Myocardial Infarction. Circulation. 2019;139(3):395–403.

108. Unverzagt S, Buerke M, de Waha A, Haerting J, Pietzner D, Seyfarth M, Thiele H, Werdan K, Zeymer U, Prondzinsky R. Intra-aortic balloon pump counterpulsation (IABP) for myocardial infarction complicated by cardiogenic shock. Cochrane Database Syst Rev. 2015;(3):CD007398.

109. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2018;39(2):119–77.

110. Werdan K, Gielen S, Ebelt H, Hochman JS. Mechanical circulatory support in cardiogenic shock. Eur Hear J. 2014;35.

111. Thiele H, Jobs A, Ouweneel DM, Henriques JPS, Seyfarth M, Desch S, Eitel I, Pöss J, Fuernau G, de Waha S. Percutaneous short-term active mechanical support devices in cardiogenic shock: a systematic review and collaborative meta-analysis of randomized trials. Eur Heart J. 2017;38(47):3523–31.

112. Peura JL, Colvin-Adams M, Francis GS, Grady KL, Hoffman TM, Jessup M, John R, Kiernan MS, Mitchell JE, O'Connell JB et al. Recommendations for the Use of Mechanical Circulatory Support: Device Strategies and Patient Selection. Circulation. 2012;126(22):2648–67.

113. Sheu J-J, Tsai T-H, Lee F-Y, Fang H-Y, Sun C-K, Leu S, Yang C-H, Chen S-M, Hang C-L, Hsieh Y-K et al. Early extracorporeal membrane oxygenator-assisted primary percutaneous coronary intervention improved 30-day clinical outcomes in patients with ST-segment elevation myocardial infarction complicated with profound cardiogenic shock. Crit Care Med. 2010;38(9):1810–7.

114. Chamogeorgakis T, Rafael A, Shafii AE, Nagpal D, Pokersnik JA, Gonzalez-Stawinski G V. Which is better: a miniaturized percutaneous ventricular assist device or extracorporeal membrane oxygenation for patients with cardiogenic shock? ASAIO J. 2013;59(6):607–11.

115. Lamarche Y, Cheung A, Ignaszewski A, Higgins J, Kaan A, Griesdale DEG, Moss R. Comparative outcomes in cardiogenic shock patients managed with Impella microaxial pump or extracorporeal life support. J Thorac Cardiovasc Surg. 2011;142(1):60–5.

116. Kawashima D, Gojo S, Nishimura T, Itoda Y, Kitahori K, Motomura N, Morota T, Murakami A, Takamoto S, Kyo S et al. Left ventricular mechanical support with Impella provides more ventricular unloading in heart failure than extracorporeal membrane oxygenation. ASAIO J. 2011;57(3):169–76.

117. Schrage B, Burkhoff D, Rübsamen N, Becher PM, Schwarzl M, Bernhardt A, Grahn H, Lubos E, Söffker G, Clemmensen P et al. Unloading of the Left Ventricle During Venoarterial Extracorporeal Membrane Oxygenation Therapy in Cardiogenic Shock. JACC Hear Fail. 2018;6(12):1035–43.

118. Patel SM, Lipinski J, Al-Kindi SG, Patel T, Saric P, Li J, Nadeem F, Ladas T, Alaiti A, Phillips A et al. Simultaneous Venoarterial Extracorporeal Membrane Oxygenation and Percutaneous Left Ventricular Decompression Therapy with Impella Is Associated with Improved Outcomes in Refractory Cardiogenic Shock. ASAIO J. 2019;65(1):21–8.

119. Arnett EN, Isner JM, Redwood DR, Kent KM, Baker WP, Ackerstein H, Roberts WC. Coronary artery narrowing in coronary heart disease: comparison of cineangiographic and necropsy findings. Ann Intern Med. 1979;91(3):350–6.

120. Wayangankar SA, Bangalore S, McCoy LA, Jneid H, Latif F, Karrowni W, Charitakis K, Feldman DN, Dakik HA, Mauri L et al. Temporal Trends and Outcomes of Patients Undergoing Percutaneous Coronary Interventions for Cardiogenic Shock in the Setting of Acute Myocardial Infarction - A Report From the CathPCI Registry. JACC Cardiovasc Interv. 2016;9(4):341–51.

121. Webb JG, Lowe AM, Sanborn TA, White HD, Sleeper LA, Carere RG, Buller CE, Wong SC, Boland J, Dzavik V et al. Percutaneous coronary intervention for cardiogenic shock in the SHOCK trial. J Am Coll Cardiol. 2003;42(8):1380–6.

122. Webb JG, Sanborn TA, Sleeper LA, Carere RG, Buller CE, Slater JN, Baran KW, Koller PT, Talley JD, Porway M et al. Percutaneous coronary intervention for cardiogenic shock in the SHOCK Trial Registry. Am Heart J. 2001;141(6):964–70.

123. Van Der Schaaf RJ, Claessen BE, Marije Vis M, Hoebers LP, Koch KT, Baan J, Meuwissen M, Engstrom AE, Kikkert J, Tijssen JGP et al. Effect of Multivessel Coronary Disease With or Without Concurrent Chronic Total Occlusion on One-Year Mortality in Patients Treated With Primary Percutaneous Coronary Intervention for Cardiogenic Shock. 2010;105(7):955–9.

124. Saad M, Fuernau G, Desch S, Eitel I, De Waha S, Pöss J, Ouarrak T, Schneider S, Zeymer U, Thiele H. Prognostic impact of non-culprit chronic total occlusions in infarct-related cardiogenic shock: Results of the randomised IABP-SHOCK II trial. EuroIntervention. 2018;14:e306-e313 published online.

125. Watanabe H, Morimoto T, Shiomi H, Kawaji T, Furukawa Y, Nakagawa Y, Ando K, Kadota K, Kimura T. Chronic total occlusion in non-infarct-related artery is associated with increased short-and long-term mortality in patients with ST-segment elevation acute myocardial infarction complicated by cardiogenic shock (from the CREDO-Kyoto AMI registry). Catheter Cardiovasc Interv. 2018;92(3):455–63.

126. Col NF, Gurwitz JH, Alpert JS, Goldberg RJ. Frequency of inclusion of patients with cardiogenic shock in trials of thrombolytic therapy. Am J Cardiol. 1994;73(2):149–57.

127. Holmes DR, Bates ER, Kleiman NS, Sadowski Z, Horgan JH, Morris DC, Califf RM, Berger PB, Topol EJ. Contemporary reperfusion therapy for cardiogenic shock: the GUSTO-I trial experience. The GUSTO-I Investigators. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. J Am Coll Cardiol. 1995;26(3):668–74.

128. Prewitt RM, Gu S, Schick U, Ducas J. Effect of a mechanical vs a pharmacologic increase in aortic pressure on coronary blood flow and thrombolysis induced by IV administration of a thrombolytic agent. Chest. 1997;111(2):449–53.

129. Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2016;37(3):267–315.

130. Hochman JS, Sleeper LA, Webb JG, Sanborn TA, White HD, Talley JD, Buller CE, Jacobs AK, Slater JN, Col J et al. Early Revascularization in Acute Myocardial Infarction Complicated by Cardiogenic Shock. N Engl J Med. 1999;341(9):625–34.

131. Hochman JS, Sleeper LA, Webb JG, Al. E. Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction. JAMA. 2006;295(21):2511–5.

132. Urban P, Stauffer J-C, Bleed D, Khatchatrian N, Amann W, Bertel O, van den Brand M, Danchin N, Kaufmann U, Meier B et al. A randomized evaluation of early revascularization to treat shock complicating acute myocardial infarction. The (Swiss) Multicenter Trial of Angioplasty for Shock—(S)MASH. Eur Heart J. 1999;20(14):1030–8.

133. Bangalore S, Gupta N, Guo Y, Lala A, Balsam L, Roswell RO, Reyentovich A, Hochman JS. Outcomes with Invasive vs Conservative Management of Cardiogenic Shock Complicating Acute Myocardial Infarction. Am J Med. 2015;128(6):601–8.

134. Aissaoui N, Puymirat E, Tabone X, Charbonnier B, Schiele F, Lefevre T, Durand E, Blanchard D, Simon T, Cambou J-P et al. Improved outcome of cardiogenic shock at the acute stage of myocardial infarction: a report from the USIK 1995, USIC 2000, and FAST-MI French Nationwide Registries. Eur Heart J. 2012;33(20):2535–43.

135. Kolte D, Khera S, Dabhadkar KC, Agarwal S, Aronow WS, Timmermans R, Jain D, Cooper HA, Frishman WH, Menon V et al. Trends in Coronary Angiography, Revascularization, and Outcomes of Cardiogenic Shock Complicating Non–ST-Elevation Myocardial Infarction. Am J Cardiol. 2016;117(1):1–9.

136. Scholz KH, Maier SKG, Maier LS, Lengenfelder B, Jacobshagen C, Jung J, Fleischmann C, Werner GS, Olbrich HG, Ott R et al. Impact of treatment delay on mortality in ST-segment elevation myocardial infarction (STEMI) patients presenting with and without haemodynamic instability: results from the German prospective, multicentre FITT-STEMI trial. Eur Heart J. 2018;39(13):1065–74.

137. Kochar A, Al-Khalidi HR, Hansen SM, Shavadia JS, Roettig ML, Fordyce CB, Doerfler S, Gersh BJ, Henry TD, Berger PB et al. Delays in Primary Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction Patients Presenting With Cardiogenic Shock. JACC Cardiovasc Interv. 2018;11(18):1824–33.

138. Kawaji T, Shiomi H, Morimoto T, Furukawa Y, Nakagawa Y, Kadota K, Ando K, Mizoguchi T, Abe M, Takahashi M et al. Long-term clinical outcomes in patients with ST-segment elevation acute myocardial infarction complicated by cardiogenic shock due to acute pump failure. Eur Hear J Acute Cardiovasc Care. 2018;7(8):743–54.

139. Wald DS, Morris JK, Wald NJ, Chase AJ, Edwards RJ, Hughes LO, Berry C, Oldroyd KG. Randomized Trial of Preventive Angioplasty in Myocardial Infarction. N Engl J Med. 2013;369(12):1115–23.

140. Smits PC, Abdel-Wahab M, Neumann F-J, Boxma-de Klerk BM, Lunde K, Schotborgh CE, Piroth Z, Horak D, Wlodarczak A, Ong PJ et al. Fractional Flow Reserve-Guided Multivessel Angioplasty in Myocardial Infarction. N Engl J Med. 2017;376(13):1234–44.

141. Gershlick AH, Khan JN, Kelly DJ, Greenwood JP, Sasikaran T, Curzen N, Blackman DJ, Dalby M, Fairbrother KL, Banya W et al. Randomized Trial of Complete Versus Lesion-Only Revascularization in Patients Undergoing Primary Percutaneous Coronary Intervention for STEMI and Multivessel Disease. J Am Coll Cardiol. 2015;65(10):963–72.

142. Lee JM, Rhee TM, Hahn JY, Kim HK, Park J, Hwang D, Choi KH, Kim J, Park TK, Yang JH et al. Multivessel Percutaneous Coronary Intervention in Patients With ST-Segment Elevation Myocardial Infarction With Cardiogenic Shock. J Am Coll Cardiol. 2018;71(8):844–56.

143. Park JS, Cha KS, Lee DS, Shin D, Lee HCHW, Oh J-H, Kim JSJH, Choi JH, Park YH, Lee HCHW et al. Culprit or multivessel revascularisation in ST-elevation myocardial infarction with cardiogenic shock. Heart. 2015;101(15):1225–32.

144. Mylotte D, Morice M-C, Eltchaninoff H, Garot J, Louvard Y, Lefèvre T, Garot P. Primary percutaneous coronary intervention in patients with acute myocardial infarction, resuscitated cardiac arrest, and cardiogenic shock: the role of primary multivessel revascularization. JACC Cardiovasc Interv. 2013;6(2):115–25.

145. Yang JH, Hahn J-Y, Song PS, Song Y Bin, Choi S-H, Choi J-H, Lee SH, Jeong M-H, Choi D-J, Kim YJ et al. Percutaneous coronary intervention for nonculprit vessels in cardiogenic shock complicating ST-segment elevation acute myocardial infarction. Crit Care Med. 2014;42(1):17–25.

146. Bauer T, Zeymer U, Hochadel M, Möllmann H, Weidinger F, Zahn R, Nef HM, Hamm CW, Marco J, Gitt AK. Use and outcomes of multivessel percutaneous coronary intervention in patients with acute myocardial infarction complicated by cardiogenic shock (from the EHS-PCI Registry). Am J Cardiol. 2012;109(7):941–6.

147. Cavender MA, Rajeswaran J, DiPaola L, Houghtaling P, Kiernan MS, Rassi AN, Menon V, Whitlow PW, Ellis SG, Shishehbor MH. Outcomes of culprit versus multivessel PCI in patients with multivessel coronary artery disease presenting with ST-elevation myocardial infarction complicated by shock. J Invasive Cardiol. 2013;25(5):218–24.

148. Zeymer U, Werdan K, Schuler G, Zahn R, Neumann F-J, Fürnau G, de Waha S, Schneider S, Thiele H. Impact of immediate multivessel percutaneous coronary intervention versus culprit lesion intervention on 1-year outcome in patients with acute myocardial infarction complicated by cardiogenic shock: Results of the randomised IABP-SHOCK II. Eur Hear J Acute Cardiovasc Care. 2017;6(7):601–9.

149. de Waha S, Jobs A, Eitel I, Pöss J, Stiermaier T, Meyer-Saraei R, Fuernau G, Zeymer U, Desch S, Thiele H. Multivessel versus culprit lesion only percutaneous coronary intervention in cardiogenic shock complicating acute myocardial infarction: A systematic review and meta-analysis. Eur Hear J Acute Cardiovasc Care. 2018;7(1):28–37.

150. Kolte D, Sardar P, Khera S, Zeymer U, Thiele H, Hochadel M, Radovanovic D, Erne P, Hambraeus K, James S et al. Culprit Vessel–Only Versus Multivessel Percutaneous Coronary Intervention in Patients With Cardiogenic Shock Complicating ST-Segment–Elevation Myocardial Infarction. Circ Cardiovasc Interv. 2017;10(11):e005582.

151. Thiele H, Akin I, Sandri M, Fuernau G, de Waha S, Meyer-Saraei R, Nordbeck P, Geisler T, Landmesser U, Skurk C et al. PCI Strategies in Patients with Acute Myocardial Infarction and Cardiogenic Shock. N Engl J Med. 2017;377(25):2419–32.

152. Thiele H, Akin I, Sandri M, de Waha-Thiele S, Meyer-Saraei R, Fuernau G, Eitel I, Nordbeck P, Geisler T, Landmesser U et al. One-Year Outcomes after PCI Strategies in Cardiogenic Shock. N Engl J Med. 2018;379(18):1699–710.

153. Lindholm MG, Boesgaard S, Thune JJ, Kelbaek H, Andersen HR, Kober L, DANAMI-2 investigators. Percutaneous coronary intervention for acute MI does not prevent in-hospital development of cardiogenic shock compared to fibrinolysis. Eur J Heart Fail. 2008;10(7):668–74.

154. White HD, Assmann SF, Sanborn TA, Jacobs AK, Webb JG, Sleeper LA, Wong C-K, Stewart JT, Aylward PEG, Wong S-C et al. Comparison of Percutaneous Coronary Intervention and Coronary Artery Bypass Grafting After Acute Myocardial Infarction Complicated by Cardiogenic Shock: results from the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) . Circulation. 2005;112(13):1992–2001.

155. TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) Trial. N Engl J Med. 1985;312(14):932–6.

156. Huang R, Sacks J, Thai H, Goldman S, Morrison DA, Barbiere C, Ohm J. Impact of stents and abciximab on survival from cardiogenic shock treated with percutaneous coronary intervention. Catheter Cardiovasc Interv. 2005;65(1):25–33.

157. Sabaté M, Räber L, Heg D, Brugaletta S, Kelbaek H, Cequier A, Ostojic M, Iñiguez A, Tüller D, Serra A et al. Comparison of Newer-Generation Drug-Eluting With Bare-Metal Stents in Patients With Acute ST-Segment Elevation Myocardial Infarction. JACC Cardiovasc Interv. 2014;7(1):55–63.

158. Sabaté M, Brugaletta S, Cequier A, Iñiguez A, Serra A, Jiménez-Quevedo P, Mainar V, Campo G, Tespili M, den Heijer P et al. Clinical outcomes in patients with ST-segment elevation myocardial infarction treated with everolimus-eluting stents versus bare-metal stents (EXAMINATION): 5-year results of a randomised trial. Lancet. 2016;387(10016):357–66.

159. Jaguszewski M, Ghadri J-R, Seifert B, Hiestand T, Herrera P, Gaemperli O, Landmesser U, Maier W, Nallamothu BK, Windecker S et al. Drug-eluting stents vs. bare metal stents in patients with cardiogenic shock: a comparison by propensity score analysis. J Cardiovasc Med. 2015;16(3):220–9.

160. Ledwoch J, Fuernau G, Desch S, Eitel I, Jung C, de Waha S, Poess J, Schneider S, Schuler G, Werdan K et al. Drug-eluting stents versus bare-metal stents in acute myocardial infarction with cardiogenic shock. Heart. 2017;103(15):1177–84.

161. Levy MS, Moussa ID. Transradial PCI in cardiogenic shock, the final frontier? Catheter Cardiovasc Interv. 2011;78(6):886–7.

162. Mamas MA, Anderson SG, Ratib K, Routledge H, Neyses L, Fraser DG, Buchan I, de Belder MA, Ludman P, Nolan J et al. Arterial access site utilization in cardiogenic shock in the United Kingdom: is radial access feasible? Am Heart J. 2014;167(6):900-8.e1.

163. Rodriguez-Leor O, Fernandez-Nofrerias E, Carrillo X, Mauri J, Oliete C, Rivas M del C, Bayes-Genis A. Transradial percutaneous coronary intervention in cardiogenic shock: A single-center experience. Am Heart J. 2013;165(3):280–5.

164. Pancholy SB, Palamaner Subash Shantha G, Romagnoli E, Kedev S, Bernat I, Rao S V, Jolly S, Bertrand OF, Patel TM. Impact of access site choice on outcomes of patients with cardiogenic shock undergoing percutaneous coronary intervention: A systematic review and meta-analysis. Am Heart J. 2015;170(2):353–61.

165. Mason PJ, Shah B, Tamis-Holland JE, Bittl JA, Cohen MG, Safirstein J, Drachman DE, Valle JA, Rhodes D, Gilchrist IC et al. An Update on Radial Artery Access and Best Practices for Transradial Coronary Angiography and Intervention in Acute Coronary Syndrome: A Scientific Statement From the American Heart Association. Circ Cardiovasc Interv. 2018;11(9):e000035.

166. Orban M, Mayer K, Morath T, Bernlochner I, Hadamitzky M, Braun S, Schulz S, Hoppmann P, Hausleiter J, Tiroch K et al. Prasugrel vs clopidogrel in cardiogenic shock patients undergoing primary PCI for acute myocardial infarction. Results of the ISAR-SHOCK registry. Thromb Haemost. 2014;112(6):1190–7.

167. Orban M, Limbourg T, Neumann F-J, Ferenc M, Olbrich H-G, Richardt G, Hennersdorf M, Empen K, Fuernau G, Desch S et al. ADP receptor antagonists in patients with acute myocardial infarction complicated by cardiogenic shock: a post hoc IABP-SHOCK II trial subgroup analysis. EuroIntervention. 2016;12(11):e1395–403.

168. Giri S, Mitchel J, Azar RR, Kiernan FJ, Fram DB, McKay RG, Mennett R, Clive J, Hirst JA. Results of primary percutaneous transluminal coronary angioplasty plus abciximab with or without stenting for acute myocardial infarction complicated by cardiogenic shock. Am J Cardiol. 2002;89(2):126–31.

169. Antoniucci D, Valenti R, Migliorini A, Moschi G, Trapani M, Dovellini E V, Bolognese L, Santoro GM. Abciximab therapy improves survival in patients with acute myocardial infarction complicated by early cardiogenic shock undergoing coronary artery stent implantation. Am J Cardiol. 2002;90(4):353–7.

170. Chan AW, Chew DP, Bhatt DL, Moliterno DJ, Topol EJ, Ellis SG. Long-term mortality benefit with the combination of stents and abciximab for cardiogenic shock complicating acute myocardial infarction. Am J Cardiol. 2002;89(2):132–6.

171. Droppa M, Vaduganathan M, Venkateswaran R V, Singh A, Szumita PM, Roberts RJ, Qamar A, Hack L, Rath D, Gawaz M et al. Cangrelor in cardiogenic shock and after cardiopulmonary resuscitation: A global, multicenter, matched pair analysis with oral P2Y12 inhibition from the IABP-SHOCK II trial. Resuscitation. 2019;137:205–12.

172. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, van den Brand M, Van Dyck N, Russell ME, Mohr FW et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention. 2005;1(2):219–27.

173. Serruys PW, Morice M-C, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Ståhle E, Feldman TE, van den Brand M, Bass EJ et al. Percutaneous Coronary Intervention versus Coronary-Artery Bypass Grafting for Severe Coronary Artery Disease. N Engl J Med. 2009;360(10):961–72.

174. Kim YH, Park DW, Kim WJ, Lee JY, Yun SC, Kang SJ, Lee SW, Lee CW, Park SW, Park SJ. Validation of SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score for prediction of outcomes after unprotected left main coronary revascularization. JACC Cardiovasc Interv. 2010;3(6):612–23.

175. Garg S, Serruys PW, Silber S, Wykrzykowska J, van Geuns RJ, Richardt G, Buszman PE, Kelbæk H, van Boven AJ, Hofma SH et al. The Prognostic Utility of the SYNTAX Score on 1-Year Outcomes After Revascularization With Zotarolimus- and Everolimus-Eluting Stents: A Substudy of the RESOLUTE All Comers Trial. JACC Cardiovasc Interv. 2011;4(4):432–41.

176. Wykrzykowska JJ, Garg S, Girasis C, de Vries T, Morel MA, van Es GA, Buszman P, Linke A, Ischinger T, Klauss V et al. Value of the SYNTAX score for risk assessment in the all-comers population of the randomized multicenter LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) trial. J Am Coll Cardiol. 2010;56(4):272–7.

177. Magro M, Räber L, Heg D, Taniwaki M, Kelbaek H, Ostojić M, Baumbach A, Tüller D, von Birgelen C, Roffi M et al. The MI SYNTAX score for risk stratification in patients undergoing primary percutaneous coronary intervention for treatment of acute myocardial infarction: A substudy of the COMFORTABLE AMI trial. Int J Cardiol. 2014;175(2):314–22.

178. Palmerini T, Genereux P, Caixeta A, Cristea E, Lansky A, Mehran R, Dangas G, Lazar D, Sanchez R, Fahy M et al. Prognostic Value of the SYNTAX Score in Patients With Acute Coronary Syndromes Undergoing Percutaneous Coronary Intervention: Analysis From the ACUITY (Acute Catheterization and Urgent Intervention Triage StrategY) Trial. J Am Coll Cardiol. 2011;57(24):2389–97.

179. Hayıroğlu Mİ, Keskin M, Uzun AO, Bozbeyoğlu E, Yıldırımtürk Ö, Kozan Ö, Pehlivanoğlu S. Predictive value of SYNTAX score II for clinical outcomes in cardiogenic shock underwent primary percutaneous coronary intervention; a pilot study. Int J Cardiovasc Imaging. 2018;34(3):329–36.

180. Lin MJ, Chen CY, Lin HD, Wu HP. Prognostic Analysis for Cardiogenic Shock in Patients with Acute Myocardial Infarction Receiving Percutaneous Coronary Intervention. Biomed Res Int. 2017;2017:8530539.

181. Genereux P, Palmerini T, Caixeta A, Rosner G, Green P, Dressler O, Xu K, Parise H, Mehran R, Serruys PW et al. Quantification and impact of untreated coronary artery disease after percutaneous coronary intervention: the residual SYNTAX (Synergy Between PCI with Taxus and Cardiac Surgery) score. J Am Coll Cardiol. 2012;59(24):2165–74.

182. Witberg G, Lavi I, Assali A, Vaknin-Assa H, Lev E, Kornowski R. The incremental impact of residual SYNTAX score on long-term clinical outcomes in patients with multivessel coronary artery disease treated by percutaneous coronary interventions. Catheter Cardiovasc Interv. 2015;86(1):3–10.

183. Park KW, Kang J, Kang S-H, Ahn H-S, Kang H-J, Koo B-K, Chae I-H, Youn T-J, Oh B-H, Park Y-B et al. The impact of residual coronary lesions on clinical outcomes after percutaneous coronary intervention: Residual SYNTAX score after percutaneous coronary intervention in patients from the Efficacy of Xience/Promus versus Cypher in rEducing Late Loss after. Am Heart J. 2014;167(3):384-392.e5.

184. Malkin CJ, George V, Ghobrial MS, Krishnan A, Siotia A, Raina T, Morton AC, Gunn J. Residual SYNTAX score after PCI for triple vessel coronary artery disease: quantifying the adverse effect of incomplete revascularisation. EuroIntervention. 2013;8(11):1286–95.

185. Farooq V, Serruys PW, Bourantas C V, Zhang Y, Muramatsu T, Feldman T, Holmes DR, Mack M, Morice MC, Stahle E et al. Quantification of incomplete revascularization and its association with five-year mortality in the synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) trial validation of the residual SYNTAX score. Circulation. 2013;128(2):141–51.

186. Xu B, Yang YJ, Han YL, Lu SZ, Li B, Liu Q, Zhu GY, Cui JY, Li L, Zhao YL et al. Validation of residual SYNTAX score with second-generation drug-eluting stents: one-year results from the prospective multicentre SEEDS study. EuroIntervention. 2014/03/08. 2014;10(1):65–73.

187. Alidoosti M, Saroukhani S, Lotfi-Tokaldany M, Jalali A, Sobh-Rakhshankhah A. Objectifying the level of incomplete revascularization by the residual SYNTAX score and evaluating its impact on the one-year outcome of percutaneous coronary intervention in patients with multi-vessel disease. Cardiovasc Revasc Med. 2016/05/21. 2016;17(5):308–12.

188. Jang WJ, Yang JH, Song YB, Hahn JY, Choi JH, Chun WJ, Oh JH, Park YH, Kim WS, Lee YT et al. Clinical implications of residual SYNTAX score after percutaneous coronary intervention in patients with chronic total occlusion and multivessel coronary artery disease: a comparison with coronary artery bypass grafting. EuroIntervention. 2017;13(1):97–105.

189. Malkin CJ, Ghobrial MSA, Raina T, Siotia A, Morton AC, Gunn J. Impact of incomplete revascularization in patients undergoing PCI for unprotected left main stem stenosis. Catheter Cardiovasc Interv. 2013;81(6):939–46.

190. Mehta RH, Harjai KJ, Grines L, Stone GW, Boura J, Cox D, O'Neill W, Grines CL, Primary Angioplasty in Myocardial Infarction (PAMI) Investigators. Sustained ventricular tachycardia or fibrillation in the cardiac catheterization laboratory among patients receiving primary percutaneous coronary intervention. J Am Coll Cardiol. 2004;43(10):1765–72.

191. Morris F, Brady WJ. ABC of clinical electrocardiography: Acute myocardial infarction-Part I. BMJ. 2002;324(7341):831–4.

192. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD. Third universal definition of myocardial infarction. J Am Coll Cardiol. 2012;60(16):1581–98.

193. Di Diego JM, Antzelevitch C. Acute myocardial ischemia: Cellular mechanisms underlying ST segment elevation. J Electrocardiol. 2014;47(4):486–90.

194. Katz A. The ischemic heart. In: Physiology of the heart. 5th Editio. Katz A, editor. Lippincott Williams & Wilkins, Philadelphia, U.S.; 2006. 522–545 p.

195. Fisch C. Electrocardiography. In: Braunwald E, editor. Heart Disease. W.B. Saunders Co, Philadelphia, PA; 1997. p. 108–52.

196. Yan G-X, Lankipalli RS, Burke JF, Musco S, Kowey PR. Ventricular repolarization components on the electrocardiogram: cellular basis and clinical significance. J Am Coll Cardiol. 2003;42(3):401–9.

197. Willis Hurst J. Thoughts About the Abnormalities in the Electrocardiogram of Patients with Acute Myocardial Infarction with Emphasis on a More Accurate Method of Interpreting S-T Segment Displacement: Part II. Clin Cardiol. 2007;30(9):443–9.

198. Nable JV, Brady W. The evolution of electrocardiographic changes in ST-segment elevation myocardial infarction. Am J Emerg Med. 2009;27(6):734–46.

199. Dressler W, Roesler H. High T waves in the earliest stage of myocardial infarction. Am Heart J. 1947;34(5):627–45.

200. Perera D, Patel SJ, Redwood SR. Dynamics of ST Segment in Ischaemic Heart Disease. In: Malik M, Camm A, editors. Dynamic Electrocardiography (1st ed). Oxford, UK: Blackwell Publishing; 2004 [cited 2019 Apr 9]. p. 222.

201. Blanke H, Cohen M, Schlueter GU, Karsch KR, Rentrop KP. Electrocardiographic and coronary arteriographic correlations during acute myocardial infarction. Am J Cardiol. 1984;54(3):249–55.

202. Zimetbaum PJ, Josephson ME. Use of the Electrocardiogram in Acute Myocardial Infarction. N Engl J Med. 2003;348(10):933–40.

203. Haim M, Hod H, Reisin L, Kornowski R, Reicher-Reiss H, Goldbourt U, Boyko V, Behar S. Comparison of Short- and Long-Term Prognosis in Patients With Anterior Wall Versus Inferior or Lateral Wall Non-Q-Wave Acute Myocardial Infarction. Am J Cardiol. 1997;79(6):717–21.

204. Thanavaro S, Kleiger RE, Province MA, Hubert JW, Miller JP, Krone RJ, Oliver GC. Effect of infarct location on the in-hospital prognosis of patients with first transmural myocardial infarction. Circulation. 1982;66(4):742–7.

205. Li D, Li CY, Yong AC, Kilpatrick D. Source of electrocardiographic ST changes in subendocardial ischemia. Circ Res. 1998;82(9):957–70.

206. Levine HD, Ford R V. Subendocardial infarction; report of six cases and critical survey of the literature. Circulation. 1950;1(2):246–63.

207. Nikus KC, Eskola MJ. Electrocardiogram patterns in acute left main coronary artery occlusion. J Electrocardiol. 2008;41(6):626–9.

208. Nikus KC, Sclarovsky S, Huhtala H, Niemelä K, Karhunen P, Eskola MJ. Electrocardiographic presentation of global ischemia in acute coronary syndrome predicts poor outcome. Ann Med. 2012;44(5):494–502.

209. French JK, Armstrong PW, Cohen E, Kleiman NS, O'Connor CM, Hellkamp AS, Stebbins A, Holmes DR, Hochman JS, Granger CB et al. Cardiogenic shock and heart failure post–percutaneous coronary intervention in ST-elevation myocardial infarction: Observations from "Assessment of Pexelizumab in Acute Myocardial Infarction." Am Heart J. 2011;162(1):89–97.

210. Holmes DR, Berger PB, Hochman JS, Granger CB, Thompson TD, Califf RM, Vahanian A, Bates ER, Topol EJ. Cardiogenic Shock in Patients With Acute Ischemic Syndromes With and Without ST-Segment Elevation. Circulation. 1999;100(20):2067–73.

211. Jacobs AK, French JK, Col J, Sleeper LA, Slater JN, Carnendran L, Boland J, Jiang X, LeJemtel T, Hochman JS. Cardiogenic shock with non-ST-segment elevation myocardial infarction: a report from the SHOCK Trial Registry. J Am Coll Cardiol. 2000;36(3, Supplement 1):1091–6.

212. Khera S, Kolte D, Aronow WS, Palaniswamy C, Subramanian KS, Hashim T, Mujib M, Jain D, Paudel R, Ahmed A et al. Non-ST-Elevation Myocardial Infarction in the United States: Contemporary Trends in Incidence, Utilization of the Early Invasive Strategy, and In-Hospital Outcomes. J Am Heart Assoc. 2014;3(4).

213. Francia P, Balla C, Paneni F, Volpe M. Left bundle-branch block—pathophysiology, prognosis, and clinical management. Clin Cardiol. 2007;30(3):110–5.

214. Surawicz B, Childers R, Deal BJ, Gettes LS. AHA/ACCF/HRS Recommendations for the Standardization and Interpretation of the Electrocardiogram. Part III: Intraventricular Conduction Disturbances A Scientific Statement From the American Heart Association Electrocardiography and Arrhythmias Committee, . J Am Coll Cardiol. 2009;53(11):976–81.

215. Haataja P, Nikus K, Kähönen M, Huhtala H, Nieminen T, Jula A, Reunanen A, Salomaa V, Sclarovsky S, Nieminen MS et al. Prevalence of ventricular conduction blocks in the resting electrocardiogram in a general population: The Health 2000 Survey. Int J Cardiol. 2013;167(5):1953–60.

216. Bussink BE, Holst AG, Jespersen L, Deckers JW, Jensen GB, Prescott E. Right bundle branch block: prevalence, risk factors, and outcome in the general population: results from the Copenhagen City Heart Study. Eur Heart J. 2013;34(2):138–46.

217. Fernandez-Lozano I, Brugada J. Right bundle branch block: are we looking in the right direction? Eur Heart J. 2013;34(2):86–8.

218. Breithardt G, Breithardt O-A. Left bundle branch block, an old-new entity. J Cardiovasc Transl Res. 2012;5(2):107–16.

219. de Bakker JM, van Capelle FJ, Janse MJ, Tasseron S, Vermeulen JT, de Jonge N, Lahpor JR. Slow conduction in the infarcted human heart. “Zigzag” course of activation. Circulation. 1993;88(3):915–26.

220. Sandler H, Dodge HT. Left ventricular tension and stress in man. Circ Res. 1963;13:91–104.

221. Petrov DB. Appearance of right bundle branch block in electrocardiograms of patients with pulmonary embolism as a marker for obstruction of the main pulmonary trunk. J Electrocardiol. 2001;34(3):185–8.

222. Bacharova L, Szathmary V, Mateasik A. QRS complex and ST segment manifestations of ventricular ischemia: the effect of regional slowing of ventricular activation. J Electrocardiol. 2013;46(6):497–504.

223. Hackel DB, Wagner G, Ratliff NB, Cies A, Estes EH. Anatomic studies of the cardiac conducting system in acute myocardial infarction. Am Heart J. 1972;83(1):77–81.

224. Futami C, Tanuma K, Tanuma Y, Saito T. The arterial blood supply of the conducting system in normal human hearts. Surg Radiol Anat. 2003;25(1):42–9.

225. Frink RJ, James TN. Normal blood supply to the human His bundle and proximal bundle branches. Circulation. 1973;47(1):8–18.

226. Elizari M V., Acunzo RS, Ferreiro M. Hemiblocks revisited. Vol. 115, Circulation. 2007. p. 1154–63.

227. Pérez-Riera AR, Barbosa-Barros R, Daminello-Raimundo R, de Abreu LC, Tonussi Mendes JE, Nikus K. Left posterior fascicular block, state-of-the-art review: A 2018 update. Vol. 18, Indian Pacing and Electrophysiology Journal. Indian Pacing and Electrophysiology Group; 2018. p. 217–30.

228. Selvester RH, Wagner NB, Wagner GS. Ventricular excitation during percutaneous transluminal angioplasty of the left anterior descending coronary artery. Am J Cardiol. 1988;62(16):1116–21.

229. Van de Werf F, Ardissino D, Betriu A, Cokkinos D V., Falk E, Fox KAA, Julian D, Lengyel M, Neumann F-J, Ruzyllo W et al. Management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2003;24(1):28–66.

230. Tolppanen H. Prognostication in Acute Heart Failure and Cardiogenic Shock - Focus on Electrocardiography and Biomarkers. Helsingin yliopisto; 2019.

231. Sgarbossa EB, Pinski SL, Gates KB, Wagner GS. Predictors of in-hospital bundle branch block reversion after presenting with acute myocardial infarction and bundle branch block. Am J Cardiol. 1998;82(3):373–4.

232. Sugiura T, Iwasaka T, Hasegawa T, Matsutani M, Takahashi N, Takayama Y, Inada M. Factors associated with persistent and transient fascicular blocks in anterior wall acute myocardial infarction. Am J Cardiol. 1989;63(12):784–7.

233. Jensen MT, Pereira M, Araujo C, Malmivaara A, Ferrieres J, Degano IR, Kirchberger I, Farmakis D, Garel P, Torre M et al. Heart rate at admission is a predictor of in-hospital mortality in patients with acute coronary syndromes: Results from 58 European hospitals: The European Hospital Benchmarking by Outcomes in acute coronary syndrome Processes study. Eur Hear J Acute Cardiovasc Care. 2018;7(2):149–57.

234. Mehta RH, Califf RM, Yang Q, Pieper KS, White HD, Ohman EM, Harrington RA, Granger CB. Impact of initial heart rate and systolic blood pressure on relation of age and mortality among fibrinolytic-treated patients with acute ST-elevation myocardial infarction presenting with cardiogenic shock. Am J Cardiol. 2007;99(6):793–6.

235. Indolfi C, Ross J. The role of heart rate in myocardial ischemia and infarction: implications of myocardial perfusion-contraction matching. Prog Cardiovasc Dis. 1993;36(1):61–74.

236. Vasquez A, Kern KB, Hilwig RW, Heidenreich J, Berg RA, Ewy GA. Optimal dosing of dobutamine for treating post-resuscitation left ventricular dysfunction. Resuscitation. 2004;61(2):199–207.

237. Manz M, Reuter M, Lauck G, Omran H, Jung W. A Single Intravenous Dose of Ivabradine, a Novel I(f) Inhibitor, Lowers Heart Rate but Does Not Depress Left Ventricular Function in Patients with Left Ventricular Dysfunction. Cardiology. 2003;100(3):149–55.

238. Barillà F, Pannarale G, Torromeo C, Paravati V, Acconcia MC, Tanzilli G, Mangieri E, Dominici T, Martino F, Pannitteri G et al. Ivabradine in Patients with ST-Elevation Myocardial Infarction Complicated by Cardiogenic Shock: A Preliminary Randomized Prospective Study. Clin Drug Investig. 2016;36(10):849–56.

239. Gallet R, Ternacle J, Damy T, Guendouz S, Bremont C, Seemann A, Gueret P, Dubois-Rande J-L, Lim P. Hemodynamic effects of Ivabradine in addition to dobutamine in patients with severe systolic dysfunction. Int J Cardiol. 2014;176(2):450–5.

240. Schmitt J, Duray G, Gersh BJ, Hohnloser SH. Atrial fibrillation in acute myocardial infarction: a systematic review of the incidence, clinical features and prognostic implications. Eur Heart J. 2009;30(9):1038–45.

241. Jabre P, Roger VL, Murad MH, Chamberlain AM, Prokop L, Adnet F, Jouven X. Mortality Associated With Atrial Fibrillation in Patients With Myocardial Infarction. Circulation. 2011;123(15):1587–93.

242. Gorenek B, Blomström Lundqvist C, Brugada Terradellas J, Camm AJ, Hindricks G, Huber K, Kirchhof P, Kuck K-H, Kudaiberdieva G, Lin T et al. Cardiac arrhythmias in acute coronary syndromes: position paper from the joint EHRA, ACCA, and EAPCI task force. EP Eur. 2014;16(11):1655–73.

243. de Waha S, Schoene K, Fuernau G, Desch S, Eitel I, Pöss J, Meyer-Saraei R, Eitel C, Tilz R, Schuler G et al. Prognostic impact of atrial fibrillation in cardiogenic shock complicating acute myocardial infarction: a substudy of the IABP-SHOCK II trial. Clin Res Cardiol. 2018;107(3):233–40.

244. Ruiz Bailén M, Rucabado-Aguilar L, Castillo-Rivera AM, Expósito-Ruiz M, Morante-Valle A, Rodríguez-García JJ, Pintor-Mármol A, Galindo-Rodríguez S, Ruiz-García MI, Gómez Jiménez FJ et al. Cardiogenic shock in acute coronary syndrome in the Spanish population. Med Sci Monit. 2008;14(11):PH46-57.

245. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J. 2015;36(41):2793–867.

246. van Erven L, Schalij MJ. Amiodarone: an effective antiarrhythmic drug with unusual side effects. Heart. 2010;96(19):1593–600.

247. Bänsch D, Oyang F, Antz M, Arentz T, Weber R, Val-Mejias JE, Ernst S, Kuck K-H. Successful Catheter Ablation of Electrical Storm After Myocardial Infarction. Circulation. 2003;108(24):3011–6.

248. Nguyen HL, Lessard D, Spencer FA, Yarzebski J, Zevallos JC, Gore JM, Goldberg RJ. Thirty-year trends (1975-2005) in the magnitude and hospital death rates associated with complete heart block in patients with acute myocardial infarction: a population-based perspective. Am Heart J. 2008;156(2):227–33.

249. Gang UJO, Hvelplund A, Pedersen S, Iversen A, Jons C, Abildstrom SZ, Haarbo J, Jensen JS, Thomsen PEB. High-degree atrioventricular block complicating ST-segment elevation myocardial infarction in the era of primary percutaneous coronary intervention. Europace. 2012;14(11):1639–45.

250. Singh SM, FitzGerald G, Yan AT, Brieger D, Fox KAA, López-Sendón J, Yan RT, Eagle KA, Steg PG, Budaj A et al. High-grade atrioventricular block in acute coronary syndromes: insights from the Global Registry of Acute Coronary Events. Eur Heart J. 2015;36(16):976–83.

251. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, Cleland J, Deharo JC, Delgado V, Elliott PM et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association. Eur Hear J. 2013;34(29):2281–329.

252. Surawicz B, Childers R, Deal BJ, Gettes LS. AHA/ACCF/HRS Recommendations for the Standardization and Interpretation of the Electrocardiogram Endorsed by the International Society for Computerized Electrocardiology. J Am Coll Cardiol. 2009;53(11):976–81.

253. Zimetbaum PJ, Buxton AE, Batsford W, Fisher JD, Hafley GE, Lee KL, O'Toole MF, Page RL, Reynolds M, Josephson ME. Electrocardiographic predictors of arrhythmic death and total mortality in the multicenter unsustained tachycardia trial. Circulation. 2004;110(7):766–9.

254. Aro AL, Anttonen O, Tikkanen JT, Junttila MJ, Kerola T, Rissanen HA, Reunanen A, Huikuri H V. Intraventricular Conduction Delay in a Standard 12-Lead Electrocardiogram as a Predictor of Mortality in the General Population. Circ Arrhythmia Electrophysiol. 2011;4(5):704–10.

255. Javanainen T, Tolppanen H, Lassus J, Nieminen MS, Sionis A, Spinar J, Silva-Cardoso J, Greve Lindholm M, Banaszewski M, Harjola VP et al. Predictive value of the baseline electrocardiogram ST-segment pattern in cardiogenic shock: Results from the CardShock Study. Ann Noninvasive Electrocardiol. 2018;23(5):e1256.

256. Tolppanen H, Javanainen T, Sans-Rosello J, Parenica J, Nieminen T, Pavlusova M, Masip J, Köber L, Banaszewski M, Sionis A et al. Prevalence, Temporal Evolution, and Impact on Survival of Ventricular Conduction Blocks in Patients With Acute Coronary Syndrome and Cardiogenic Shock. Am J Cardiol. 2018;122(2):199–205.

257. Javanainen T, Sans-Roselló J, Harjola V-P, Nieminen MS, Lassus J, Sionis A, Varpula M, Jurkko R. Prognostic impact of baseline and residual SYNTAX scores in cardiogenic shock. Catheter Cardiovasc Interv. 2018;93(1):1–8.

258. Kastrati A, Neumann F-J, Schulz S, Massberg S, Byrne RA, Ferenc M, Laugwitz K-L, Pache J, Ott I, Hausleiter J et al. Abciximab and Heparin versus Bivalirudin for Non–ST-Elevation Myocardial Infarction. N Engl J Med. 2011;365(21):1980–9.

259. Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the Vulnerable Plaque. J Am Coll Cardiol. 2006;47(8):C13–8.

260. Abbott JD, Ahmed HN, Vlachos HA, Selzer F, Williams DO. Comparison of outcome in patients with ST-elevation versus non-ST-elevation acute myocardial infarction treated with percutaneous coronary intervention (from the National Heart, Lung, and Blood Institute Dynamic Registry). Am J Cardiol. 2007/07/17. 2007;100(2):190–5.

261. Polonski L, Gasior M, Gierlotka M, Osadnik T, Kalarus Z, Trusz-Gluza M, Zembala M, Wilczek K, Lekston A, Zdrojewski T et al. A comparison of ST elevation versus non-ST elevation myocardial infarction outcomes in a large registry database: Are non-ST myocardial infarctions associated with worse long-term prognoses? Int J Cardiol. 2011;152(1):70–7.

262. Rogers WJ, Frederick PD, Stoehr E, Canto JG, Ornato JP, Gibson CM, Pollack Jr C V, Gore JM, Chandra-Strobos N, Peterson ED et al. Trends in presenting characteristics and hospital mortality among patients with ST elevation and non-ST elevation myocardial infarction in the National Registry of Myocardial Infarction from 1990 to 2006. Am Heart J. 2008;156(6):1026–34.

263. Hirsch A, Verouden NJW, Koch KT, Baan Jr J, Henriques JPS, Piek JJ, Rohling WJ, van der Schaaf RJ, Tijssen JGP, Vis MM et al. Comparison of Long-Term Mortality After Percutaneous Coronary Intervention in Patients Treated for Acute ST-Elevation Myocardial Infarction Versus Those With Unstable and Stable Angina Pectoris. Am J Cardiol. 2009;104(3):333–7.

264. Chan MY, Sun JL, Newby LK, Shaw LK, Lin M, Peterson ED, Califf RM, Kong DF, Roe MT. Long-Term Mortality of Patients Undergoing Cardiac Catheterization for ST-Elevation and Non-ST-Elevation Myocardial Infarction. Circulation. 2009;119(24):3110–7.

265. Col JJ, Weinberg SL. The incidence and mortality of intraventricular conduction defects in acute myocardial infarction. Am J Cardiol. 1972;29(3):344–50.

266. Kincaid DT, Botti RE. Significance of isolated left anterior hemiblock and left axis deviation during acute myocardial infarction. Am J Cardiol. 1972;30(8):797–800.

267. Marriott HJ, Hogan P. Hemiblock in acute myocardial infarction. Chest. 1970;58(4):342–4.

268. Rizzon P, Di Biase M, Baissus C. Intraventricular conduction defects in acute myocardial infarction. Br Heart J. 1974;36(7):660–8.

269. Entezarjou A, Mohammad MA, Andell P, Koul S. Culprit vessel: impact on short-term and long-term prognosis in patients with ST-elevation myocardial infarction. Open Hear. 2018;5(2):e000852.

270. Conde-Vela C, Moreno R, Hernández R, Pérez-Vizcayno MJ, Alfonso F, Escaned J, Sabaté M, Bañuelos C, Macaya C. Cardiogenic shock at admission in patients with multivessel disease and acute myocardial infarction treated with percutaneous coronary intervention: Related factors. Int J Cardiol. 2007;123(1):29–33.

271. Fach A, Bünger S, Zabrocki R, Schmucker J, Conradi P, Garstka D, Fiehn E, Hambrecht R, Wienbergen H. Comparison of Outcomes of Patients With ST-Segment Elevation Myocardial Infarction Treated by Primary Percutaneous Coronary Intervention Analyzed by Age Groups. Am J Cardiol. 2015;116(12):1802–9.

272. Karwowski J, Poloński L, Gierlotka M, Gąsior M, Bęćkowski M, Kowalik I, Szwed H. Post-procedural TIMI flow grade 2 is not associated with improved prognosis in patients with non-ST-segment elevation myocardial infarction undergoing percutaneous coronary revascularization (PL-ACS registry). Cardiol J. 2016;23(4):402–10.

273. Brkovic V, Dobric M, Beleslin B, Giga V, Vukcevic V, Stojkovic S, Stankovic G, Nedeljkovic MA, Orlic D, Tomasevic M et al. Additive prognostic value of the SYNTAX score over GRACE, TIMI, ZWOLLE, CADILLAC and PAMI risk scores in patients with acute ST-segment elevation myocardial infarction treated by primary percutaneous coronary intervention. Int J Cardiovasc Imaging. 2013;29(6):1215–28.

274. Wit AL, Janse MJ. Reperfusion arrhythmias and sudden cardiac death: a century of progress toward an understanding of the mechanisms. Circ Res. 2001;89(9):741–3.